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MOUNT EVEREST IN UTERO*

President's Address

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SINCE the founding of the American Association on April 19, 1888, sixty-three previous presidents have stood before the Fellows and guests on this occasion and have presented a series of distinguished addresses. Of them it can be said without exaggeration that they have risen to the heights of perspicacity, erudition, and eloquence; and before them I am duly humbled. But this let me remark. Whatever else may be said of the address you are about to hear, it can always be maintained, at least in a literal sense, that it also rose to the heights, because, ladies and gentlemen, with your leave, I am going to talk to you about balloon ascensions and the Luftwaffe, about the heights of the Peruvian Andes and the stratosphere. In fact, the very title of my address is "Mount Everest in Utero," a term coined by the late Sir Joseph Barcroft. The meaning of this title and its bearing on some of the most important problems in obstetrics will become manifest, I trust, as my theme gradually develops.

The first specific evidence that the air at high altitudes is somehow different from that at sea level was recorded in 1298 by the amazing Venetian, Marco Polo,

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when crossing the lofty plateau of Pamir in Central Asia. His observations read as follows: "The plain is called Pamir, and you ride across it for twelve days altogether, finding nothing but a desert without habitations or any green thing, so that travellers are obliged to carry with them whatever they have need of. The region is so lofty and cold that you do not even see any birds flying. And I must notice also that because of this great cold, fire does not burn so brightly, nor give up so much heat as usual, nor does it cook food so effectually." Marco Polo makes no mention of respiratory difficulties or other physical complaints, but he was a very leisurely traveler and had probably become acclimated to high altitudes through increased hemoglobin formation. His explanation of the ineffectual nature of fire at this high altitude on the grounds of extreme cold was an error that was to be perpetuated, with one exception, for five hundred years.

The first descriptions of respiratory distress at high altitudes were recorded by the Spanish conquistadors in the course of their assaults on Mexico and Peru. In the year 1519, a certain Diego Ordaz, one of Cortes' captains, with nine Spaniards and several natives, undertook the ascent of Mt. Popocatepetl which, some seventy-five miles south of Mexico City, towers to the height of 17,852 feet. Prescott's classic description of this experience, based on contemporary accounts, reads in part as follows: "To increase their distress, respiration in these aerial regions became so difficult, that every effort was attended with sharp pains in the head and limbs." Because of the physical distress experienced, the attempt to scale the mountain had to be abandoned. Twenty-five years later, an army of Pizarro crossed the Andes at 13,500 feet, but underwent such frightful suffering that more than 2,000 men died while traversing the summits. Although subsequent sixteenth and seventeenth century records of mountain expeditions refer repeatedly to the severe respiratory distress experienced at high altitudes, the explanation was always the same, that is, extreme cold, fatigue, and lack of food. Prior to the beginning of the eighteenth century, indeed, no suspicion was voiced of the true nature of mountain illness except for the isolated observations made in 1590 by the Jesuit priest, DaCosta, as the result of many years spent in the Andes. His astute comments read in part as follows: "There is no doubt that the cause of this distress and strange affiiction is the wind or the air current there. . . . I am convinced that the element of the air in this place is so thin and so delicate that it is not proportioned to human breathing, which requires it denser and more temperate."

The first fairly accurate explanation of mountain sickness was the contribution of the French physician, Jourdanet, based on studies in the mountains of Mexico and published in a series of monographs in 1861 and thereafter. In passing, we may note that it was Jourdanet who first coined the term "anoxemia." For lucidity and ease of comprehension, Jourdanet's explanation of mountain sickness is exemplary and in the belief that some of his comments will lend clarity even today to our own consideration of the problem, I hope you will bear with me if I quote some of his conclusions as

follows: "The corpuscles and the barometric pressure regulate the quantity of oxygen in the blood. Since oxygen is the chief vital element, its decrease for lack of corpuscles causes the weakness of anemic patients; its decrease in the blood for lack of pressure must produce the same result. The weakness produced by bleeding is evidently the consequence of a sudden lack of oxygen through the loss of a certain quantity of corpuscles, just as mountain sickness results from a more direct withdrawal of the same gas. So that beyond a doubt, *an ascent beyond 3000 meters amounts to a barometric disoxygenation of the blood just as bleeding is a disoxygenation of the blood through the lack of corpuscles.*"

During the present century mountaineering has provided additional knowledge about the reaction of the human organism to high altitudes, of two main sorts: (1) reports emanating from the sport of mountain climbing, as exemplified by the recent attacks on Tirach Mir, Annapurna, and Mt. Everest; and (2) reports by teams of scientific experts who, after establishing temporary laboratories at moderately high altitudes, have studied the precise physiologic alterations which elevated regions produce.

One of the noteworthy findings which has emanated from the sport of mountain climbing is the frequency with which cerebral dysfunction develops at high altitudes. For example, when the 1950 Norwegian Expedition was ascending Tirach Mir and had reached a level of 20,500 feet, the leader of the expedition wrote in his log as follows: "Yesterday was very complicated and unpleasant for us. In the morning Streather's porter had an acute mental aberration. Everyone who felt fairly well had to hold him, tie him up, etc. He tore his tent to bits, and was just waiting for an opportunity to throw himself down the precipice. Besides this, everybody felt very feeble yesterday, headaches, etc. . . . We have been struggling to give the porter an injection and pour medicines into him. Morale very low this morning . . . all wanted to go down,—stomachs, heads, lassitude, depression!" In writing of his experiences at 20,000 feet, Maurice Herzog, the leader of the recent Annapurna Expedition, writes: "I was clear-headed and delirious by turns and had the queer feeling that my eyes were glazed." This same leader, it may be recalled, lost his gloves on the summit of Annapurna and made part of the descent with bare hands. As a consequence his hands froze and, tragically enough, most of his fingers had later to be amputated. To a veteran mountain climber such as Herzog it might be presumed that the loss of his gloves under such circumstances would have been a shaking, cataclysmic, never-to-be-forgotten experience. But he remembered nothing at all about it. Moreover, although he had a pair of substitute mittens in his pocket all the while which he himself had put there just in case this very accident should occur, he "forgot" to put them on. Thus, does anoxia paralyze cerebral function. We shall have occasion to hark back to this observation when we come to survey the obstetrical etiology of cerebral palsy.

Although the reports of various scientific expeditions to the Andes, Pike's Peak, and other summits have yielded observations of the utmost importance,

only one will be noted here, namely, the phenomenon of acclimatization. Here, let us recall again that the two main factors in determining the blood oxygen content are the red corpuscles, or the hemoglobin concentration, as we would now say, and the barometric pressure. Now, if one factor, let us say, the barometric pressure is reduced by a certain percentage, an increase in the other factor, that is, in the amount of hemoglobin, serves to compensate for this change. Each gram of hemoglobin would carry less oxygen, but since the number of grams is increased, the end result in respect to total oxygen available for tissue consumption remains about the same. After a person has lived at a high altitude for several weeks, this compensatory change regularly takes place in more or less degree. Studies carried out by the Luftwaffe in World War II indicate that three to four weeks are necessary for acclimatization to 10,000 feet and eleven to twelve weeks for acclimatization to 20,000 feet. The observations of John Scott Haldane, Yandell Henderson, and their associates on Pike's Peak in 1911 demonstrated that thirty-five days at 14,000 feet yield a 20 per cent increase in hemoglobin concentration and a proportionate increase in the number of red cells. We have just had occasion to mention the name of the late John Scott Haldane, the great English physiologist, whose researches in this and other fields have added so much to science. Those of you who have read of the grueling hardships experienced by mountain climbers from cold, wind, and avalanches will agree with me, I am sure, that Haldane was a mountaineer after our own hearts. In speaking to Yandell Henderson about his desire to make certain biochemical observations at high altitudes, he commented: "I want a nice comfortable, easily accessible, very high mountain with a fairly good hotel on the top." Replied Henderson: "Come to America next summer and we will spend a month or two on the top of Pike's Peak." Thus started that famous expedition.

The balloon ascension which has perhaps contributed most to our knowledge of anoxia at high altitudes is that of the balloon "Zenith" in which two balloonists, Sivel and Crocé-Spinelli, and one scientist, Tissandier, made an ascent on April 15, 1875. It had a tragic ending. The two balloonists died and Tissandier just barely survived to write a graphic description of the experience. Although these men were provided with bags of oxygen, they became so weak and disoriented at an altitude of 24,600 feet that they could not raise their hands to seize the oxygen tube. At a height of 25,247 feet, Tissandier found it impossible to speak and became unconscious. The instruments showed that the balloon ascended to 28,820 feet and then began to descend of its own accord.

The physiologist, Paul Bert, who was interested in variations of barometric pressure and their effects on bodily functions was deeply touched by the disastrous outcome of the flight of the "Zenith," but at the same time was stimulated to pursue with greater zeal his researches on the effects of variations in barometric pressure on the animal organism. In his great classic, *La Pression barometrique,* published in 1878, he showed that the diminution in barometric pressure associated with high altitudes acts upon

living beings only by lowering the oxygen pressure in the air they breathe and by exposing them thus to the dangers of asphyxiation. In other words, it is that fraction (one-fifth) of the total barometric pressure contributed by the oxygen present which determines the degree to which oxygen diffuses through the pulmonary capillaries and combines with hemoglobin—the so-called "partial pressure" of oxygen.

From aviation medicine of course a vast body of knowledge has accumulated pertinent to the subject under consideration but we shall turn to it for the answer to only one question, namely: What is the highest altitude at which man can survive without an artificial source of oxygen? Or, to put it another way: What is the lowest partial pressure of oxygen compatible with human existence? These questions cannot be answered categorically because the time over which the organism is exposed to low oxygen pressure is naturally an important factor as is also the degree of acclimatization which may have preceded the experience. We have seen, however, from the ascent of the "Zenith" that an altitude of 28,800 feet killed two of the three unacclimatized men in the balloon very promptly.

Much more extensive and detailed information on this question is provided by the study of Lewis and Haymaker on 75 fatal cases of high altitude hypoxia which occurred during World War II in the United States Army Air Force. All these deaths were due solely and unequivocally to low oxygen pressure. Twenty-three of the seventy-five deaths, or approximately one-third, occurred between 26,000 and 28,000 feet. An additional twenty-three deaths took place between 17,000 and 26,000 feet. Thus, two-thirds of the total number occurred at levels below 28,000 feet. The time prior to death during which these men were without supplemental oxygen could not be ascertained in 30 cases, but in the remaining 45 it was established fairly accurately. In these 45 cases, with only two exceptions, the length of time during which these men were without supplemental oxygen was less than 30 minutes. Accordingly, on the basis of these data of Lewis and Haymaker, it can be stated with sound documentation that an altitude of 28,000 feet usually kills human beings within 30 minutes, unless they are acclimatized or provided with oxygen equipment. This, it may be noted, is well under the level of Mt. Everest for which the most authoritative figure seems to be 29,141 feet.

Having reviewed at some length certain facts about hypoxia at high altitudes, let me hasten to say that this was not done for the sake of embellishment, but rather to provide a background against which to pose the following question: If you were asked to choose an optimum environment for the fetus in utero, would you select one in which the available oxygen corresponds to that on the summit of Mt. Everest? To push the question even further, would you in your wildest dreams choose an environment for the unborn baby in which the partial pressure of oxygen corresponds to a level three quarters of a mile above Mt. Everest—corresponds, that is, to a level of 33,000 feet at which the partial pressure of oxygen is only 40 mm. Hg, a

level which we know would kill husky adults within a few minutes? The logical answer to these questions would seem so obvious that even to pose them to an intelligent audience is something of an affront. Yet, Nature in her wisdom, or, if you will, natural selection in its infinite experience, has chosen to defy what you and I would consider logical and has provided the baby in utero with an oxygen environment which corresponds not just with that on Mt. Everest but with that which exists three-quarters of a mile above the summit of Everest at the level mentioned of 33,000 feet. Incredible as this circumstance may appear, it has been documented by scores of studies over the past quarter of a century and is an accepted fact by all students of the subject.

This extraordinary oxygen environment of the fetus will become more understandable when it is recalled that in all placental mammals, because of certain diffusion gradients, fetal tissues must necessarily exist under oxygen pressures which are decidedly lower than those enjoyed by the maternal tissues. In the mother, the head of oxygen pressure which the arterial blood carries in leaving the lungs is virtually the same as that in the inspired air, that is, a little over 100 mm. Hg. But in passing through the circulation, capillary disbursement of oxygen lowers this head of pressure so that the oxygen pressure of the mixed arterial and venous blood in the capillaries is only 70 mm. Hg, or about two-thirds of the original figure. Now, since the blood in the intervillous spaces of the placenta, like capillary blood, is a mixture of arterial and venous elements, the highest oxygen pressure which could reasonably be anticipated for the fetus is this level of 70 mm. Hg. But this is not all. The already reduced head of oxygen pressure must now diffuse through the several layers of the chorionic villi; and, since oxygen is known to diffuse through any wet membrane slowly, the head of pressure is reduced still further before it reaches the blood in the chorionic capillaries. By analyzing the oxygen in the fetal arterial blood as it leaves the placenta in the umbilical vein, it is possible to calculate very accurately the oxygen pressure to which that blood has been exposed and in the human being that figure is 35 to 40 mm. Hg, or one-third that to which adult blood is exposed in the pulmonary capillaries. The previous comparison made between the oxygen environment of the fetus and that just above Everest is based on these figures, the oxygen pressure at 33,000 feet being about 39 mg. Hg.

How does the fetus manage to live and grow in such an environment? It does so presumably by several adaptations, the most noteworthy of which is a pronounced increase in hemoglobin, the very same process of acclimatization which occurs in extrauterine organisms at high altitudes. Indeed, it has been said that mountaineers are able to develop this protective mechanism because they have already learned to do so in utero. The average concentration of hemoglobin in the blood at birth is approximately 17 Gm. per 100 c.c., a figure approximately 20 per cent higher than that which obtains in the average adult or older child. This is about the degree of acclimatization which Haldane and Henderson found that residents at 14,000 feet had

developed after a month or so. The fetal blood also resembles that of mountaineers in showing other evidence of increased bone marrow activity, namely, the presence of nucleated red cells, polychromatophilia, anisocytosis, and poikilocytosis—changes which, like the increased hemoglobin concentration, disappear in the first few weeks of extrauterine life. As a still further protective mechanism, fetal hemoglobin is of an especial kind and is of such a nature that it gives off oxygen more readily than does hemoglobin of adults and older children.

Although these adaptations elucidate to a certain degree the ability of the fetus to withstand low oxygen pressures, several allied problems remain complete enigmas. For example, as a consequence of these oxygen relationships, the fetus exists in a continuous state of cyanosis, a fact that is not only documented by countless blood oxygen studies but is plainly apparent at any cesarean section. The degree of cyanosis is such that it is rarely seen in extrauterine life and, when it does occur, the subject is frantically gasping for breath; in addition, he is usually moribund. Yet, under what would seem to be comparable blood oxygen relationships, the thoracic cage of the fetus remains relatively quiescent and exhibits at the most shallow and intermittent excursions. Here is an enigma that has defied explanation for three-quarters of a century and still awaits solution. Then, too, why is the carbonic anhydrase of the fetal blood so extremely low? This enzyme, which accelerates the release of carbon dioxide from the blood, shows a concentration (in arbitrary units) of only 0.8 in premature infants, of 1.4 in full-term infants, and of 3.5 in adults. In view of the known role which carbon dioxide plays in respiration, the low concentration of this enzyme in fetal blood must be of some significance but this also is a puzzle. Other enigmas of fetal physiology might also be cited but enough has been said to show what a fairyland this is for research. But he who would storm its ramparts must not come to the attack empty-handed, because any modicum of success in this field demands a sound background in physical and enzyme chemistry as well as in the general physiology of respiration. Yet would it not be worth while?

Because of the processes of acclimatization which we have described, together perhaps with other unknown factors, the fetus appears to thrive on the low oxygen pressures normally provided for it. Unfortunately, however, because of certain vagaries of uterine contractility and placental behavior, this meager oxygen supply is sometimes depressed even lower than usual; and this the fetus cannot endure for more than a few minutes. Thus, even an average uterine contraction lasting, let us say, a minute and a half, produces temporary fetal anoxia as evidenced by the invariable slowing of the fetal heartbeat. Now, if this same contraction should last five minutes (as sometimes happens, alas, from the injudicious use of oxytocic drugs) it is well known that the fetus usually dies forthwith from anoxia. Fetal anoxia from varying degrees of placental separation, from asphyxiating anesthetics, and from compression of the umbilical cord are other familiar

examples of this disorder, any one of which may be responsible for death either in utero or in the early neonatal period. Although the causes of infant death in association with the birth process are often obscure, there is general agreement that by far the most common known cause is anoxia. In this connection Edith Potter writes as follows: "The principal cause of death before birth and in the first few weeks of extra-uterine life is interference with oxygenation. If anoxia were to be given as the cause of death of every fetus and young infant it would be correct as the immediate cause in almost all instances."

The number of infants who die in the United States every year in association with the birth process is approximately 150,000. This makes up more than one-tenth of the total number of deaths occurring in this country annually from all causes and at all ages. It is true that two other categories of disease are responsible for a larger number of deaths, that is, cardiovascular conditions and malignant neoplasms, the figure for the former approximating 600,000 and for the latter 200,000 deaths annually. Many of us here, no doubt, have lost a father, or a mother, or some other relative from one of these diseases and know full well the suffering and the anguish they cause; and certainly neither you nor I would wish to minimize the dire problem they present or would begrudge one penny of the money being spent on their study. Nevertheless, in fairness to all concerned, I should like to make these two comments. The first is this: According to data published by the National Cancer Institute of the United States Public Health Service, the average age of persons suffering from carcinoma at the time of the initial diagnosis is 58 years. What is the average life expectancy of United States citizens who are 58 years old? As shown by the most authoritative actuarial statistics, it is 16 years. And, by comparison, what is the life expectancy in the United States today of a newborn baby? Basing our statement on the same actuarial data, it is 62 years, 62 years moreover, which span the prime of life, which span the decades of greatest vigor, initiative, and achievement. The second comment I wish to make has to do with the amount of money being spent for research in these various fields. On the basis of an analysis made by Deignan and Miller for the National Research Council and published in *Science,* March 28, 1952, the government and the larger foundations awarded 12,923 grants during the period 1946-1951. The total reported for cancer was $26,389,761 and for cardiovascular diseases $11,832,433. The total reported for the newborn was included under the broad heading, "Pregnancy and Newborn." This is understandable because almost all research on pregnancy, normal or abnormal, has a bearing on the outcome for the infant. For instance, investigations of nutrition in pregnancy, of the toxemias, and more intimately of the Rh problem, all have as one of their objectives, the improvement of fetal and neonatal outlook. Hence, it is necessary to include all these obstetrical investigations and state the over-all figure for grants awarded for research on pregnancy and the newborn. This figure was $1,795,655. This is one-fifteenth the amount allotted to cancer research and

one-seventh the amount awarded to investigations of cardiovascular diseases. These ratios may well be defensible; and in any event I should prefer that you draw your own conclusions. The conclusions you do draw will depend in large part on how you assess life's values. They will depend in goodly measure on the relative values you put on the life of a 1-minute-old baby and that of a 58-year-old man or woman.

But there is perhaps an even greater tragedy than the actual death of a newborn baby. That is the birth of a baby whose brain never develops, who continues, like a vegetable, to grow and develop physically, but who lacks the cerebral centers which govern speech, muscular coordination, and reason. The incidence of this condition, cerebral palsy, is much higher than most obstetricians would probably suspect. In a study conducted in 1948 by Levin, Brightman, and Burtt in Schenectady County, New York, an incidence was encountered of 5.9 cases per 1,000 liveborn infants who survived one month. This means that in any obstetrical service, let us say, with 3,000 deliveries annually, about 18 of the babies born each year will develop cerebral palsy. The very first observation published on cerebral palsy stressed the etiological importance of the birth process. Thus, the two early papers by Little, one published in 1853 and the other in 1863, emphasized parturition as the main causative factor, the title of his second paper being: "On the Influence of Abnormal Parturitions, Difficult Labors, Premature Births and Asphyxia Neonatorum on the Physical and Mental Condition of the Child, Especially in Relation to Deformities." Ever since the publication of Little's observations, there has been widespread debate concerning the etiological factors concerned, but the preponderance of opinion has leaned toward Little's original view that parturition is an important causative agent. More recently opinion has veered toward the belief that the main etiological factor is intrauterine anoxia whether intra partum or ante partum. This viewpoint is supported by Windle's experimental research, by the neuropathological observations of Courville, and by several clinical studies.

Quite recently Doris Latham and George W. Anderson of our institution have searched through the records of several Maryland clinics for cerebral palsy and have found 61 cases in which children afflicted with this disease had been born in our hospital. They then went back and analyzed the obstetrical histories of these cases. The prenatal records of the mothers showed that there was irregular and repeated vaginal bleeding, both early and late, in a disproportionately high percentage of these pregnancies. The vascillating and prolonged degrees of anoxia which the immature fetal brain might suffer under such circumstances can easily be visualized. Eighteen, or 30 per cent, of these children with cerebral palsy had been born prematurely, three times our usual incidence of prematurity. Second stages in excess of three hours occurred six times more often in the cerebral palsy group than in the clinic population as a whole.

Another finding in the birth records of these 61 children with cerebral palsy was that their condition at birth was described as "poor" in 33 cases,

or over half. In other words, on retrospect, it is apparent that half of these children who had cerebral palsy gave evidence at birth of intrauterine damage. Provided that such a child survives at all, the outward evidence of the damage is usually transitory and after a few hours or a few days, the infant begins to behave and grow in what seems to be a normal fashion; and no one suspects that some of his most important cerebral centers are dead and defunct. It is only when the child reaches that age when it first has need of these centers for speech, coordinated locomotion, and reasoning that the tragedy becomes manifest. This is why the diagnosis of cerebral palsy is rarely made until the third or fourth year of life, at a time when any obstetrical factors are likely to be forgotten. This sequence of events is reduplicated in its entirety by Windle's experiments in guinea pigs asphyxiated at birth. These experiments were devised so as to simulate the conditions of infants born anoxic. Many of these fetuses showed obvious brain damage and neurological aberrations during the early neonatal period, but after a few weeks they lost these more obvious defects and were apparently like the normal controls. However, permanent impairment of learning ability was demonstrated in these animals by various comparative tests such as the maze tests. Windle demonstrated moreover that after the anoxic fetuses attained adulthood they learned more slowly and forgot more quickly than the controls. The highest brain centers were thus the ones most permanently damaged.

We have already noted that mountain climbers are likely to experience various mental aberrations and clouding of the reasoning faculties when above 20,000 feet. At altitudes of about 14,000 feet and above, balloonists and aviators (unless protected by artificial oxygen) experience progressive deterioration of voluntary muscular control and coordination with the result that their handwriting, try as they will, becomes illegible. Here, accordingly, is other evidence that the cerebrum is one of the first structures injured by anoxia. Knowing as we do that intrauterine anoxia actually kills such a large number of infants, would it not be logical to believe that sometimes the degree of anoxia may not be quite sufficient to kill the infant but enough to inflict irreparable injury to the cerebrum? The point here is that obstetricians and neurologists alike should be giving more attention to possible obstetrical factors in the causation of cerebral palsy in the hope that the number of these pitiful cases may be reduced.

If any tragedy compares to that of a child with cerebral palsy, it is a blind child. From 10 to 20 per cent of babies who weigh less than 3½ pounds at birth become blind within the next year as the result of the disease, retrolental fibroplasia. Statistics indicate that this disorder is today one of the commonest causes of blindness in children. One of the leading investigators of this disease, the ophthalmologist, T. S. Szewczyk, writes about its etiology as follows: "Retrolental fibroplasia is an example of a response of immature neural tissue to anoxia. This anoxia may exist primarily because of inadequate oxygenation of the blood or be induced by exposing a premature to an environment of higher oxygen concentration and withdrawing him so

rapidly that the physiological changes of acclimatization cannot take place before irreparable harm is done to rapidly developing areas such as the retina of the eye.'' The important studies of Paul Bruns and Lloyd Shields have shown that the pulmonary hyaline membrane of the newborn, one of the commonest causes of death in premature infants, may be of similar etiology. There has been introduced therefore this concept that sudden shifts in oxygen pressures may produce irreparable damage to tissues, especially to immaturely developed tissues. In view of the low oxygen tensions to which the infant has become accustomed before birth, it is understandable that oxygen therapy shortly after birth at extremely high and vascillating pressures might well have injurious effects.

Here then is Mt. Everest in utero. Here are the same sparse oxygen pressures and the same phenomena of acclimatization occurring alike in the fetus and on the heights of the Himalayas. Here is Mt. Everest and more, because in utero, as a result of certain pathological states, the already scant oxygen supply is sometimes reduced even further to levels which kill or maim untold myriads of infants. The record of obstetrics during the past few decades is one to evoke gratification and pride. But obstetrics must look to the future if it is to continue to serve the best interests of our mothers and children. For the sake of the four million potential United States citizens born every year, can you think of any subject more worthy of study than this one of Mt. Everest in utero?

ADVANCED EXTRAUTERINE PREGNANCY*

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I AM not unconscious of the very great honor which your President has conferred upon me by asking me to deliver the Joseph Price Oration before you this evening on the occasion of the Sixty-fourth Annual Meeting of your Association. I am all the more sensible of this honor when I realize that I am speaking to a body of men who have made vast and outstanding contributions to our present-day knowledge of obstetrics and gynecology.

First, may I say how proud I am to be able to pay tribute this evening to the memory of Joseph Price. His is a name which is known and honored on both sides of the Atlantic Ocean, for he belonged to that group of gynecologists and abdominal surgeons who made history during the two closing decades of the last century. Those were the days when surgery was coming into its own following upon the advent of antisepsis and asepsis, when gynecology was emerging as a specialty in its own right and when operative gynecology, in particular, was making progress of an entirely unprecedented nature. Ovarian cysts, vesicovaginal fistulas, uterine fibroids, pelvic inflammatory processes, and ruptured tubal pregnancies yielded one after the other to the growing efficiency of the surgical approach. When one considers the names of some of the great figures in American Gynecology who dominated the horizon in the days of Joseph Price, one may indeed say that "there were giants in the land in those days."

The contributions of Joseph Price himself to the newer knowledge were of the highest possible order. One has only to glance at a list of his publications to realize the breadth of his interest. There is no doubt that Joseph Price of Philadelphia was the greatest exponent of his day of the surgical treatment of inflammatory pelvic conditions such as pyosalpinx and pelvic abscess. He established the value of salpingectomy and of pelvic drainage in the appropriate cases. But he made other contributions too: he introduced certain improvements and refinements into the technique of myomectomy, he was interested in carcinoma of the urethra, and he made outstanding additions to the existing knowledge on extrauterine pregnancy. He wrote upon abdominal pregnancy and on intraligamentous pregnancy. I also think I am right in saying that, in the first volume of the Transactions of this Association, no fewer than 49 pages were devoted to discussions upon extrauterine pregnancy and that Joseph Price himself took a prominent part in these discus-

*The Joseph Price Oration for 1953, delivered at the Sixty-fourth Annual Meeting of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons, Hot Springs, Va., Sept. 10, 11, and 12, 1953.

sions. It was, in fact, the realization that Joseph Price took such a great interest in the problems of extrauterine pregnancy that led me to a decision as to the subject of my address to you this evening.

Another influence which guided me in my choice was the fact that during more than twenty-five years of work in China and Hong Kong I have had the good fortune to meet with twelve cases of advanced extrauterine pregnancy, comprising examples of nearly all of the well-recognized types. As these cases are seldom encountered in these days of early surgical treatment, I thought that it might be of interest if I spoke to you on the subject of "Advanced Extrauterine Pregnancy." I shall always remember the first patient of my series coming to see me one day, bringing with her what she thought was a chicken bone which she had passed per rectum, but which on further investigation proved to be a fetal femur. The last of my series came to me in April of this year, just as I was beginning to regret the fact that I had not a round dozen of cases to present to you.

One of the earliest descriptions of advanced extrauterine pregnancy was written nearly a thousand years ago by Albucasis, who was generally regarded as the greatest surgeon of the Arabic era of medicine. Albucasis flourished at Cordova in Spain during the tenth century (936-1013), as the physician to Caliph Abdur-Rahman III. His treatise on surgery was regarded as a standard work in medieval times; it was first published in Venice in 1497 shortly after the advent of printing, and a later edition was produced in Oxford by John Channing in the year 1779, so that for several hundred years it wielded a dominating influence in the realm of Surgery. I have ventured to make a translation of the following passage from the Latin of John Channing's edition, in which Albucasis describes one of the well-known terminations of secondary abdominal pregnancy. He says:

> On one occasion I saw a woman who became pregnant and the fetus died within her. After that she conceived a second time and this other fetus also died. It so chanced that, after a long time, a swelling developed in her umbilical region which became more and more distended until it burst open and pus came forth. I had been called in to look after her and I attended her for a considerable length of time, but the opening did not heal. I therefore applied to her certain ointments which had a powerful drawing-out effect. Eventually a bone was passed out from the opening, and after the lapse of several days yet another bone made its appearance. I was greatly astonished at this as the belly is a place which contains no bones and I therefore formed the opinion that these bones came from the dead fetus. Consequently, I investigated the wound and extracted from it many bones. As for the woman, she made an excellent recovery and, moreover, she continued in the best of health for a long time, with but a slight discharge of pus from the sinus.

From the time of Albucasis until the beginning of the nineteenth century there were numerous references to isolated but interesting examples of advanced extrauterine pregnancy, but no detailed study was made of the various types and no classification was suggested. A most valuable guide to the rather confused literature of this period is the *Genealogy of Gynaecology* by James V. Ricci, a truly monumental work which is quite indispensable to one studying the history of gynecology throughout the ages. Most of the well-known cases of advanced extrauterine pregnancy encountered before the end of the

sixteenth century were referred to in that remarkable compendium of gynecological knowledge produced in 1597 by Israel Spach of Strasbourg under the title of the *Gynaeciorum*. This formidable quarto volume of more than one thousand pages, written partly in Greek but mainly in Latin, was the forerunner of the modern textbook by multiple authors and contained contributions by such men as Caspar Bauhin, Felix Platerus, and Mauricius Cordaeus, all of whom had experience of abdominal pregnancy. In the section written by Bauhin details are given of the celebrated case of the wife of Jacob Nufer, a case which is of interest to us this evening because it is probable that this was an example, not of a classical cesarean section, but of an extrauterine pregnancy at term, an opinion which has been upheld by several writers. I give the following translation of Bauhin's original account:

> In the year 1500 Elizabeth, wife of Jacob Nufer, a swine-gelder of the village of Sigershausen, in Switzerland, was pregnant with her first child. After suffering from the pains of labor for several days she called to her aid thirteen midwives, one after the other, and several lithotomists. But she looked to them for help in vain, for neither could they deliver her of the child, nor could they alleviate her suffering. As the pains again became very severe and as there remained no other hope of relieving her, the husband told his wife that, if she agreed, he would like to try his own efforts upon her because he hoped, if God so willed, that it might lead to a happy outcome. The woman replied that she was prepared to undergo any ordeal. As the matter was a delicate one, the husband went off to the chief magistrate of the district to explain the matter and ask for permission to undertake the attempt. When he understood the problem the chief magistrate at first, indeed, showed himself rather difficult but eventually he trusted in the assurance of the husband and gave his consent to the performance of the proposed operation. The husband, having returned home, told the midwives that those who had the courage to assist him could remain in the chamber, but that the more timid ones would have to retire, as he was going to attempt something which he hoped, in the providence of God, would save the life of his wife. Eleven of the midwives withdrew after they understood his intention and marvelled at it, but two of the more plucky ones remained with the lithotomists to take their stand by the woman in labor. And so, having first sought divine aid and carefully closed the door, the husband placed his wife upon a table and made an incision in her belly, just as he would have done in the swine. He opened the abdomen so neatly with one stroke of his knife that the child was extracted at once without harm. When the eleven midwives who remained outside heard the cries of the infant they vainly implored to be allowed to come in again. But they were not admitted until after the child had been washed and the wound sewn up in the manner used by the veterinary surgeons. After this the wound healed most successfully without any complications supervening. Some time after the operation she gave birth to twins, one of whom, named John Nufer, was a magistrate in Sigershausen at the age of 60 and was still alive in his eighty-third year. After the twins she had four more children. The child delivered by the operation lived until he was 77 years of age.

If it is accepted that this was an abdominal pregnancy, then this is the first recorded example of operative delivery followed by the survival of both mother and child.

The famous Lithopedion or petrified embryo of the city of Sens was also reported in the *Gynaeciorum* by Cordaeus. In this case, which occurred during the early part of the sixteenth century, the child apparently remained within the abdomen for 31 years, and on the death of the patient at the age of 71 the fetus was found enclosed in a stony crust in the lower abdomen.

Christopher Bain's case also belongs to this period. This "travelling surgeon," according to Donatus, operated on an Italian woman in April, 1540, and extracted the skeleton of a male child. The agreed fee for this operation was to be ten golden pieces if the patient survived and her body if she died. The patient survived and had four more children. In 1545, Cornax "enlarged, by incision, an umbilical fistula and extracted a semi-putrid foetus which had been retained for four years" (Ricci). Horstius, in 1563, reported the case of a woman who had carried a child in her abdomen for 14 years. In 1584, Felix Platter extracted fetal parts in a state of putrefaction from an umbilical fistula, and the patient survived the operation. Then there was the well-authenticated case of Primerose which occurred in 1595. The patient, a woman of 30, became pregnant in March, 1591. At term she went into false labor, but the pains subsided and later menstruation reappeared. In 1594 she became pregnant again, but at eight months fetal movements ceased. In June, 1595, a fistula developed to the right of the umbilicus, from which a surgeon, Jacob Noierus, removed a dead fetus. Two months later a second swelling appeared and at a second operation another fetus was removed by Stephanus Mainaldus of Bordeaux. This is probably the first recorded case of bilateral extrauterine pregnancy.

Jean Riolan, a surgeon and anatomist of Paris, is credited with giving the first authentic description of ruptured tubal pregnancy in 1616. According to Ricci: "He reported the case of a woman, thirty-one years of age, who had been pregnant eight times. During the fourth month of her last gravidity she was seized with a sudden, sharp pain about the pelvis, which radiated to the chest. This attack occurred in January, 1604. The pain remained excruciating all night, and she died on the morning of the following day. At autopsy Riolan found the right tube to contain a foetus, while the uterus appeared normal."

During the eighteenth century further knowledge of this subject was accumulated and numerous interesting reports appeared. Take, for example, the case of Anna Mullern described by Dr. Steigertahl in the Philosophical Transactions of the Royal Society of London in 1721. Forty-six years before her death she declared herself to be with child and had all the usual signs of pregnancy. A false labor ensued, but the swelling remained until she died at the age of 94. Being firmly persuaded that there was a child inside, she desired her body to be opened after her death, and appointed her physician and her surgeon to perform this task. By the time she died in 1720, her physician had already predeceased her, so the duty of carrying out the autopsy fell to the surgeon, named Knauffen. Knauffen found within the abdomen "a hard mass of the form and size of a large nine-pin bowl," which, for want of a better instrument, he broke open with a blow from a hatchet. A clear description of a lithopedion followed, in which the integument was described as being "entirely bony."

Two years later, in 1723, Robert Houstoun described another case in the Philosophical Transactions in which he successfully diagnosed an extrauterine pregnancy and pleaded unsuccessfully with the patient to be allowed to re-

move it. He found "that her womb was of no bulk to contain a child near its time; and that its neck, of an uncommon hardness, was also closed so straitly, as not to admit even a small probe or knitting needle." Dr. Houstoun then declared that "her delivery was impossible because the child was not within the womb, but between the womb and the guts." The patient refused operation, however, and later developed a fistula in the region of the umbilicus from which she died about 5 years later. An autopsy was performed by Houstoun which proved the correctness of his diagnosis.

The first operation for the removal of an abdominal pregnancy in America was performed by John Bard in 1759 on a certain Mrs. Stagg. Details of this successful operation were conveyed, in a letter written later in the year by the New York surgeon, to Dr. John Fothergill of London. According to Parry three other operations for removal of an extrauterine fetus were performed in America before the end of the eighteenth century. Two of these operations were by Dr. William Baynham of Virginia, who operated successfully in 1791 on Mrs. Cocke, the wife of a Virginia planter, and in 1799 on a Negro woman.

During the nineteenth century three works were published which were of outstanding importance in relation to our subject. The first was William Campbell's *Memoir on Extra-uterine Gestation,* published in Edinburgh in 1840. Campbell probably succeeded in collecting nearly all of the material on extrauterine pregnancy up to his time, and his work is therefore a mine of information "from which many a quotation has been made by subsequent writers without any kind of acknowledgment." Lawson Tait's comment on this work was that it "stands as a landmark in the literature of the subject which, up to that time, seems to have been regarded more as a curiosity than as one of the most dreadful calamities to which women can be subjected."

The second work was entitled *Extra-Uterine Pregnancy* by John S. Parry of Philadelphia, and was published in 1876. This was a reasoned and scholarly presentation based on 500 cases of extrauterine pregnancy collected from many sources. This book had a great influence on the subsequent study and treatment of extrauterine pregnancy, and the early death of the author constituted a tragic loss to gynecology.

The third contribution was from the pen of Lawson Tait whose *Lectures on Ectopic Pregnancy and Pelvic Haematocele,* published in Birmingham in 1888, placed the operative treatment of ruptured tubal pregnancy on a sound footing. In this outstanding work Lawson Tait laid the basis of the modern classification of ectopic pregnancy and gave particulars of 42 cases of ruptured tubal pregnancy upon which he operated with only 2 deaths. Lawson Tait devoted a considerable portion of his work to the discussion of advanced extrauterine pregnancy. He gave a very clear description of the means by which a tubal pregnancy may rupture into the broad ligament and may go on developing as an intraligamentous pregnancy even up to full term. He discussed operative treatment and, from his experience of one disastrous case, strongly advised against any attempt at removal of such a pregnancy per vaginam. He mentioned 2 such cases which he treated by abdominal section where he was

able to remove the placenta after tying a big pedicle consisting of the remains of the tube and broad ligament. In both instances he secured living children and both of the mothers survived. He described 3 other instances where he was forced to leave the placenta in situ and where the mothers survived only after months of drainage and offensive suppuration.

Since the days of Lawson Tait advanced extrauterine pregnancy, except in certain countries and special localities, has been seen with ever diminishing frequency, partly owing to the almost universal availability of early surgical treatment and partly owing to the patient's slim chance of survival if she refuses, or is unable to obtain, surgical treatment during the early and critical stages of her condition. If, however, the patient and her pregnancy both survive the earlier weeks of development and the manifold risks of rupture or inordinate distention of the abnormally situated fetal sac it is not impossible, in the absence of surgical treatment, for the pregnancy to reach an advanced stage of development.

Classification of Extrauterine Pregnancies

Advanced extrauterine pregnancy may belong to any one of the following types:

I. Primary Ovarian Pregnancy.—This is very rare, and the possibility was, in fact, strenuously denied by British authors like Lawson Tait and Bland Sutton, although admitted by German writers such as Spiegelberg, who laid down his four well-known postulates in 1878. A considerable number of undoubted ovarian pregnancies have now been reported, several of which have gone to term. The ovary, in fact, seems to be more able to accommodate itself without rupture to the growing pregnancy than the tube, and this may account for the fact that a not inconsiderable number of full-term ovarian pregnancies and several lithopedia have been reported.

In a recent review, Baden and Heins analyzed no fewer than 90 cases of ovarian pregnancy reported up to March 1, 1951. Of these, 68 were terminated by the end of the first trimester, 11 were terminated during the second trimester, and 11 lasted into the third trimester or beyond. Of all 11 viable infants 7 were stillborn and 4 were alive at birth. Two of the viable babies were grossly deformed.

II. Primary Peritoneal (or Abdominal) Pregnancy.—Some people still believe, with Lawson Tait, that primary abdominal pregnancy does not occur, and there is no doubt that many of the earlier reported cases were examples of secondary abdominal pregnancy. There is, however, no a priori reason why an ovum "wrecked upon the peritoneal wastes" (in the words of Irving) should not occasionally be fertilized by a wandering spermatozoon and become implanted at some point within the general peritoneal cavity and subsequently develop to term. Reifferscheid, in 1922, described a 6 weeks' pregnancy attached to the mesentery of the sigmoid colon, while Vara found an ovum attached to a pelvic endometrioma which had undergone decidual changes. Four very unusual cases were described by F. K. King where postoperative separation of a cesarean section wound had occurred and subsequent pregnancies were abdominal, the ovum being implanted in the omentum in three cases and on the anterior abdominal wall in the fourth.

III. Primary Tubal Pregnancy.—While the great majority of primary tubal pregnancies rupture at an early date, there have been a certain number

of cases recorded where the tube has undergone progressive distention up to the size of a full-term pregnancy. There have also been at least 5 recorded cases (including one in my own series) of unruptured full-term pregnancy in the interstitial portion of the tube. In such cases it is important to demonstrate that the sac lies within the wall of the uterine cornu between the proximal end of the isthmic portion of the tube and the uterine orifice of the interstitial portion of the tube.

IV. Secondary Abdominal Pregnancy.—This is the commonest form of advanced extrauterine pregnancy and usually arises after intraperitoneal rupture or abortion of a tubal pregnancy in the event that the ovum survives and retains sufficient placental attachment for continued development. It can also follow rupture of a primary ovarian pregnancy, or further rupture of an intraligamentous pregnancy, or slow rupture of a cesarean scar. Pregnancies variously described as tubo-ovarian or tubo-abdominal are conveniently included under this heading. It is surprising how many of these cases are still being reported from various parts of the world. Cornell and Lash were able to collect 236 cases in a study which they published in 1933. And, at the Annual Meeting of this Association in 1947, H. Hudnall Ware reviewed 249 cases including 13 of his own, which occurred between the years 1933 and 1946.

V. Intraligamentous Pregnancy.—This condition is brought about when a tubal pregnancy ruptures between the folds of the broad ligament. It was well described by Dezeimeris as the "sous peritoneo-pelvienne" variety and by Tait and Werth as the extraperitoneal or intraligamentous form of pregnancy. In frequency this variety is encountered next most commonly after secondary abdominal pregnancy. Anterior and posterior forms of intraligamentous pregnancy have been described. As the gestation advances the peritoneum of the broad ligament is stripped up and the gestation sac comes into very close relationship with the pelvic colon and rectum posteriorly, with the bladder and anterior abdominal wall anteriorly, and with the vagina mesially.

Fate of the Extrauterine Fetus

There is a very high incidence of abnormality in the extrauterine fetus. Mall found only 16 normal embryos out of 117 specimens, and concluded that not more than 1 per cent of extrauterine fetuses would be capable of reaching full term, even if the vascular requirements for their survival were present. If the fetus reaches maturity under the adverse conditions which surround it, there are several further possibilities which may be summarized as follows:

1. Survival of Child.—Operative delivery offers a fair chance of survival in the relatively small number of cases where the condition is recognized and abdominal section is carried out while the child is still viable. Howard Kelly collected 77 cases of operation for ectopic viable fetuses during the years 1809-1896. The maternal mortality rate was over 50 per cent but 27 of the babies were living after one month. Only 8 of the children survived for a year or more and 2 were alive at the ages of 7½ and 15 years, respectively. It is of interest to us here tonight that Kelly's series of cases included a patient operated on by Joseph Price on March 30, 1887, at Camden, New Jersey. The patient was suffering from an abdominal pregnancy and a living child of 7½ months was delivered, that unfortunately died of prematurity four hours later. Beck made a careful study of the viable child and collected from the literature, during the years 1809-1919, 262 cases of extrauterine pregnancy, all living and older than 5 months. He found that 39.6 per cent of 202 infants survived when the operation was carried out between the twenty-

eighth and the fortieth week and that 56.6 per cent of 60 infants survived when the operation was performed between the thirty-sixth and the thirty-eighth week. In Hellman and Simon's series there were 316 babies alive at birth, although only 158 of them lived 8 days or longer. In Hudnall Ware's more recent series of 251 cases 60 of the babies survived. Living children have also been reported by Beacham and Beacham, Gardner and Middlebrook, Julius Jarcho, O'Connell, and a number of others.

2. Death of the child may take place before term is reached as a result of hemorrhage or inadequacy of the placental circulation. More commonly death takes place at term or shortly after, following false labor or unsuccessful attempts at the induction of labor. Operative removal of the child at this stage or at any one of the succeeding stages is commonly reported.

3. Maceration.—This change follows rapidly after the death of the fetus. Spalding's sign is soon manifest and absorption of the liquor amnii commences with noticeable shrinkage in the size of the sac.

4. Suppuration is very likely to take place, especially in intraligamentous pregnancies, on account of their close proximity to the bowel. After infection has gained access to the fetal sac the entire contents of the sac disintegrate and the fetus undergoes skeletonization. Eventually the bones of the fetus will ulcerate through the rectum, vagina, bladder, or anterior abdominal wall after the fashion described by many of the ancient writers, and in more recent times by Cullen, Mahfouz Pasha, Stock, and others.

5. Mummification and Adipocere Formation.—These are changes that may take place in the fetus if suppuration fails to occur. In adipocere formation the fetus becomes transformed into a greasy, greenish-yellow substance, the nature of which is not completely understood.

6. Calcification and Lithopedion Formation.—This has been variously estimated as occurring in from 1.5 to 3 per cent of extrauterine fetuses. Schumann gave the lower figure and Mahfouz Pasha gave 3 per cent as his experience. Masson and Simon reported 9 lithopedia in 445 extrauterine pregnancies in the Mayo Clinic, an incidence of 2 per cent. Since the publication by Cordaeus of his report on the famous Lithopedion of Sens in the sixteenth century some 247 cases have been described according to Brandman. Kuechenmeister, in 1881, drew attention to the fact that the process of calcification may not be limited to the child alone, but may involve the placenta and the membranes. On this basis he proposed the following classification which has been generally accepted:

a. Lithokelyphos in which calcification is limited to the membranes, the fetus remaining relatively unchanged or mummified or skeletonized. This occurs in about 26 per cent of cases.

b. Lithokelyphopedion in which both fetus and membranes and placenta are more or less impregnated with calcium salts. The amniotic fluid escapes and the fetus becomes partially or completely adherent to the sac. This is found to take place in about 31 per cent of cases.

c. True lithopedion (or lithotecnon) is still the commonest form encountered and accounts for some 43 per cent of cases. In this form the fetus alone is calcified and it is particularly likely to occur if the fetus escapes unattached into the abdominal cavity.

Features of the Present Series of Twelve Cases

The chief features of my own series of 12 cases have been summarized in Table I.

TABLE I. TWELVE CASES OF ADVANCED EXTRAUTERINE PREGNANCY

CASE NO.	AGE	PERIOD OF GESTATION	TYPE OF PREGNANCY		MOTHER	CHILD
			PRIMARY	SECONDARY		
1	35	57 weeks	L. tubal	L. intraligamentous	Alive	Skeletonized
2	37	42 weeks	R. tubal	Abdominal	Alive	Dead
3	29	38 weeks	R. tubal	R. intraligamentous	Alive	Macerated
4	39	40 weeks	R. tubal	R. intraligamentous	Alive	Alive
5	58	20 years	?	?	Fatal apoplexy	Lithopedion
6	33	70 weeks	L. interstitial	Abdominal	Alive	Commencing calcification
7	45	69 weeks	L. interstitial (unruptured)	–	Alive	Commencing calcification
8	37	60 weeks	L. tubal	L. intraligamentous	Alive	Macerated
9	31	79 weeks	L. tubal (unruptured)	–	Alive	Mummified
10	38	52 weeks	R. tubal (isthmic)	Abdominal	Alive	Macerated
11	39	39 months	L. tubal	Abdominal	Alive	Mummified
12	41	47 weeks	R. tubal	Abdominal	Alive	Macerated

Frequency.—These 12 cases of advanced extrauterine pregnancy have been encountered over a period of 21 years, during which time the obstetrical services under my care have been responsible for some 60,045 normal full-term deliveries. One might therefore say that the incidence of this condition, in relation to normal full-term pregnancies, is in the region of 1 in 5,000.

Incidence in Relation to Early Extrauterine Pregnancies.—As I no longer have access to the detailed records of the prewar years, I have been able to study the relationship between normal full-term pregnancies and early and late extrauterine pregnancies only during the 7½ year period from January, 1946, to June, 1953.

TABLE II. RELATIONSHIP OF EXTRAUTERINE PREGNANCIES TO NORMAL PREGNANCIES

Normal full-term pregnancies	45,089
Extrauterine pregnancies (before 28th week)	203
Extrauterine pregnancies (after 28th week)	7
1 extrauterine pregnancy to 215 normal pregnancies	

This gives an incidence of approximately one extrauterine pregnancy to 215 normal pregnancies. Of the extrauterine pregnancies some 3.3 per cent were of the advanced type whereas the remaining 96.7 per cent were met with before the twenty-eighth week. There is a certain degree of fallacy about these figures, however, as many patients went to other hospitals for the treatment of the ordinary form of ruptured tubal pregnancy, whereas patients with the more unusual type of advanced extrauterine gestation tended to be referred to the University Gynaecological Clinic from a very wide area.

Age Incidence.—In Fig. 1 the age incidence of 202 cases of early extrauterine pregnancy is compared with that of 12 patients with advanced extrauterine pregnancy. The tendency to a higher age incidence in the latter group

is well shown, there being a decade of difference between the two peaks. In early extrauterine pregnancies the peak incidence is reached between the years of 26 and 30, whereas it falls between 36 and 40 for the advanced group.

Previous Pregnancies.—Only two patients in the series had had no previous pregnancies. For the remainder there was an average of 2.5 children and 0.3 abortion. There was an interval varying from 3 to 19 years between the last pregnancy and the extrauterine, the average being 9.4 years. (It should be noted that the patient who carried a lithopedion for over 20 years is excluded from this calculation.) In no case was there a history of former abdominal operation.

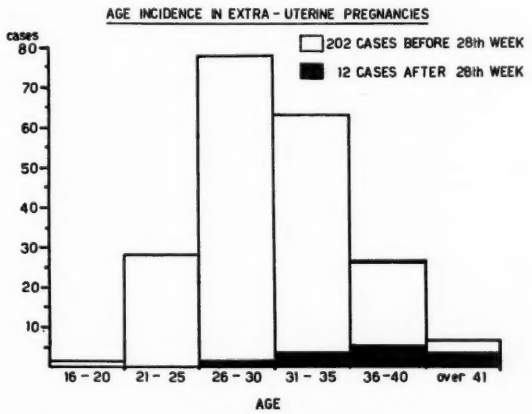

Fig. 1.—Age incidence in extrauterine pregnancy.

Duration of Extrauterine Pregnancy.—The duration of the extrauterine pregnancy in this series varied all the way from 38 weeks to over 20 years, as shown in Table I. In only one case was the fetal heart audible when the patient came under treatment, and in this case the baby was saved. In three other cases fetal death had only recently taken place, and if the patients had come under treatment a little earlier, living babies might have been obtained. In the remaining 8 cases the fetus had been dead for weeks, months, or years; and in at least 3 of these cases calcification of varying degrees had occurred.

Clinical Manifestations.—The clinical manifestations of these cases may be grouped under five separate headings, according to the stages through which the pregnancy passes:

a. The symptoms of early pregnancy must be considered first. Nearly all the patients in the group were able to identify a time when they thought they were pregnant because of the onset of amenorrhea, together with nausea and vomiting, breast changes, and other manifestations associated with early pregnancy.

b. A phase of threatened or actual rupture of the ectopic pregnancy was apparent in at least half of the patients in the series. A very clear history of this was obtained in 6 of the cases at intervals varying from the sixth to the sixteenth week of the pregnancy. The actual time of the onset of the symptoms was:

6th week	1 case
7th week	1 case
8th week	2 cases
12th week	1 case
16th week	1 case

The actual symptoms complained of were pelvic pain in 6 cases and vaginal bleeding in 3 cases, followed in all instances by the development of a pelvic or lower abdominal swelling, according to the evidence of the patient. In no case, however, was there a history suggestive of severe intra-abdominal bleeding. If these data are compared with the known time of occurrence of rupture or abortion of early tubal pregnancies in cases submitted to operation the conclusion is inescapable that the symptoms of the early weeks, recalled by patients suffering from advanced extrauterine pregnancy, were in reality those of threatened or actual rupture. Fig. 2 shows the date of operative interference (in weeks) in 203 cases of early extrauterine pregnancy. In practically all of these cases, the indication for operation was tubal rupture or abortion or hemorrhage of more or less severe degree, and it will be noticed that the date of the onset of the catastrophe corresponds very clearly with the time of the onset of symptoms in the 6 cases mentioned above.

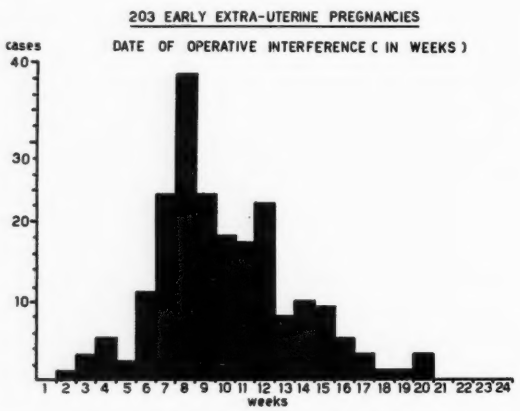

Fig. 2.—Date of operative interference in 203 early extrauterine pregnancies.

CASE 1.—A good example of the points just mentioned is to be found in this case. The patient complained of the sudden onset of pain in the left lower part of the abdomen followed by pain in the left shoulder about 6 weeks after the beginning of her amenorrhea. There was no vaginal bleeding, but a few days later a tender swelling developed in the left lower quadrant and extrauterine pregnancy was actually diagnosed by her physician and an operation advised. The patient sought the advice of another doctor, however, who told her that she had a normal pregnancy and that the pain was due to worms. A vermicide was given and the patient promptly passed 5 round worms! The pain became less, but never entirely disappeared, and a few weeks later fetal movements became noticeable and the fetal heart was heard by the physician who made the diagnosis of worms. The patient went to term, had a false labor and several days later passed a uterine cast, after which fetal movements ceased. About a month later blood appeared in the stools and there was constant abdominal pain with frequent and painful stools. The patient developed a low-grade fever, lost much weight, and her general condition deteriorated very seriously. After this had gone on for about three months the patient passed a bone per rectum which she thought was a chicken bone, but which was actually identified as a fetal femur, and she was admitted to hospital. It was then found that she had a left ligamentous pregnancy following rupture of the left tube. After the death

of the fetus, infection of the sac had taken place, the fetus had become disintegrated and an aminocolic fistula had formed, through which fetal bones were commencing to discharge. An x-ray film revealed a "bag of bones" in the pelvis and lower abdomen, and a barium enema showed that the pelvic colon was raised up by this mass, and that there was a large fistula communicating with the sac. At operation nearly all the bones of the fetal skeleton were recovered from a gestation sac situated in the left broad ligament and filled with fetal remnants and foul fecal material (Fig. 3). The operation was done extraperitoneally and after the cavity had been marsupialized for 26 days a secondary closure was undertaken of what was virtually a huge colostomy opening. The patient made an uninterrupted recovery.

c. Symptoms of continuation of the pregnancy supervene on the symptoms suggestive of rupture in those patients who do not present themselves for operative treatment and who do not succumb to the effects of the rupture. The

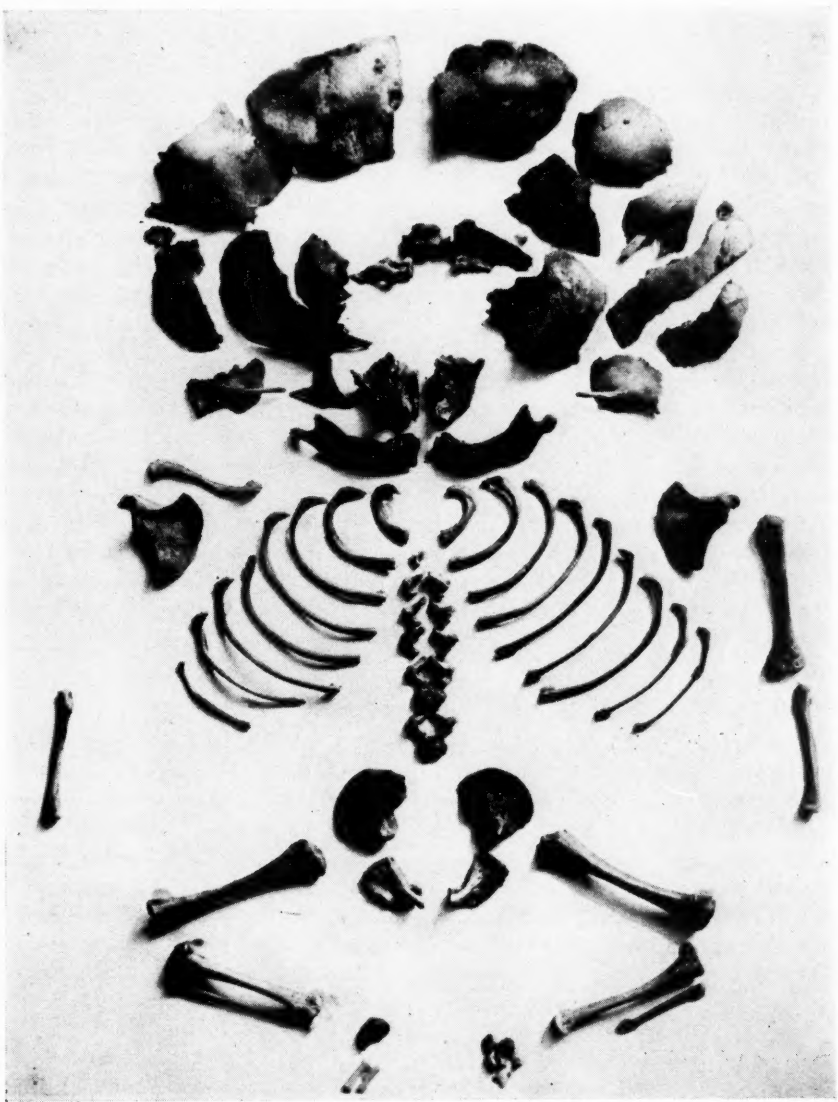

Fig. 3.—Advanced extrauterine pregnancy occupying left broad ligament with subsequent development of amniocolic fistula. With the exception of the left femur (which was passed per rectum) all the above bones were recovered from the fetal sac at operation.

vast majority of patients seek hospital treatment before they reach this stage, and, of those who do not, only a very small proportion would ever survive to develop an advanced extrauterine pregnancy. The chance of survival was easier to estimate in the days before surgery was accepted, and was very fairly put by Parry in 1876 when he said, "From a careful examination of this subject it must be acknowledged that a happy termination of the rupture of the cyst is extremely rare. . . . Of 149 cases in which the ovum was located in that portion of the tube which does not traverse the tissues of the uterus, 145 died." This is equivalent to a mortality of just over 97 per cent, and our present discussion is concerned with that small and not altogether fortunate group of less than 3 per cent of survivors. With the exception of Case 5, in whom no history was obtainable, all of my patients spoke of gradually increasing abdominal enlargement. Fetal movements were felt in 10 of them, and in 4 of them the fetal heart was said to have been heard by an attending doctor. Some of the patients complained that fetal movements were often painful.

d. A history of false labor was obtained in 6 of my cases, and in 5 of them a uterine cast was passed. False labor set in at 38 weeks in one patient and was as late as 47 weeks in another, but in the remaining 4 cases it was in the region of the fortieth week. The history of Case 12 is typical in this respect.

This patient, a Chinese woman of 41, who had been married since the age of 16 and had never had any previous pregnancy, came to the hospital on March 31, 1953, stating that she believed herself to be about 10 months pregnant, but that for the last 7 weeks she had no longer felt any fetal movements. The last menstrual period was at the commencement of June, 1952, and the patient complained of nausea, dizziness, and morning sickness during the second and third months of pregnancy. Toward the end of the third month she had an attack of cramplike pain in the lower abdomen lasting for a few days and followed by a dull aching pain for 2 or 3 weeks. Fetal movements were first felt at about the end of the fourth month and persisted for nearly five months. About 7 weeks before admission the patient had a severe attack of spasmodic abdominal pain lasting for several hours, which she thought signified the onset of labor, but the pains passed off without any further incident. Fetal movements stopped about 2 weeks after this and about a week later (i.e., 4 weeks before admission) she noticed some vaginal bleeding on awakening. There was some mild aching pain in the lower abdomen and a few hours later she passed a small mass of whitish tissue from the vagina. This patient proved to have a secondary abdominal pregnancy originating from a ruptured right tubal pregnancy, which was successfully removed at operation.

There were 2 other patients in whom labor was induced at term on the supposition that the pregnancy was intrauterine.

In Case 2, for example, medical induction was carried out twice without success. When the patient was over term a third attempt to induce labor was made, this time by means of bougies. It was found that the smallest bougie could not enter the uterine cavity for more than a very short distance. Furthermore no membranes could be demonstrated and no presenting part could be felt within the uterus. For the first time extrauterine pregnancy was suspected, and further examination under anesthesia confirmed this diagnosis. The uterus was found to be slightly enlarged, firm, and separate from the fetal sac, being situated below and to the left of the head of the fetus. The uterine cavity was found to be quite empty and would admit a sound only for a distance of 3½ inches in a direction pointing backward and to the left. The fetus occupied a large sac which appeared to be fixed in the region of the right iliac fossa. The vertex was presenting, but the head was floating above the brim of the pelvis, and rather displaced toward the right iliac fossa. The fetal heartbeat, which had previously been quite clear, had now disappeared, and was not heard again. At operation a secondary abdominal pregnancy was found arising from a ruptured right tubal pregnancy. In this case it was regrettable that the diagnosis had not been made a few hours earlier, as in that event a living baby would almost certainly have been obtained.

In Case 3, there was a somewhat similar history. The patient was 38 weeks pregnant and said that fetal movements had disappeared for the last 4 weeks. Medical induction of labor had already been carried out 3 times at another hospital without success. The fetus was presenting as a breech and vaginal examination did not give rise to the suspicion that the pregnancy might be extrauterine. An x-ray film showed a pronounced Spalding's sign, but did not suggest any doubt as to the intrauterine nature of the pregnancy. A diagnosis of fetal death in utero was made and medical induction was repeated, but again failed. Finally surgical induction by means of rubber bougies was attempted, and it then became apparent that the uterus contained a small empty cavity measuring only a little over 3 inches in length, situated below and to the left of the fetal sac. Extrauterine pregnancy was then diagnosed and immediate laparotomy was carried out.

At operation an intraligamentous pregnancy was found on the right side. The sac contained a macerated fetus, approximately 35 cm. in length, together with a thin, flattened placenta adherent to the inner surface of the sac. Removal of the entire sac was attended by little hemorrhage as the placental circulation had ceased some 4 weeks before operation.

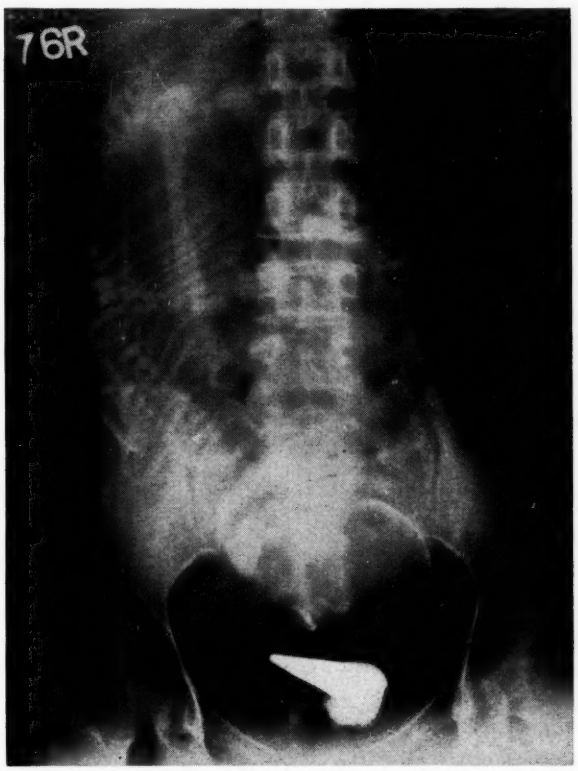

Fig. 4.—Hysterosalpingogram showing deviation of the uterine cavity (containing cannula) to the right side.

It is worthy of note that the uterus, when it can be palpated separately from the extrauterine mass, is usually slightly enlarged, perhaps up to the size of a 2½ or 3 months' pregnancy, inasmuch as it undergoes the same physiological changes which accompany normal pregnancy, even though it contains nothing but decidua. The cervix is often elongated and is not as soft as one would expect with normal pregnancy. The os is not so easily dilatable as in normal intrauterine pregnancy, a fact which soon becomes obvious if at-

tempts are made to induce labor by mechanical means. Displacement of the uterus to one side is also frequently present, and is well seen in Fig. 4 from Case 9.

e. Later clinical manifestations may be very diverse and may be spread out over a period of weeks or months or years, depending upon the length of time that elapses before the patient's condition is diagnosed and treated. The cessation of fetal movements and the passage of a cast have already been mentioned. Diminution in the size of the abdomen next takes place as the liquor amnii becomes absorbed and various secondary changes occur in the fetus. An abdominal swelling is then left which possesses several unusual characteristics, such as excessive hardness and fixity, the presence of prominences of bonelike consistence, or of hard areas which give rise to a crepitant feeling on palpation. Occasionally, as in Case 6, the swelling is so freely movable that it simulates a pedunculated ovarian cyst. Abdominal pain is a very frequent symptom and was complained of by most of this group of patients. Bowel symptoms were present in 3, in the form of frequent stools and severe tenesmus. In 2 of these cases (Nos. 1 and 8) the pregnancy was intraligamentous in position and in Case 1 parts of the fetal skeleton actually ulcerated through into the bowel and were passed. Ulceration of bony parts may also take place through the anterior abdominal wall or into the bladder or vagina. If the fetus is long retained it may ultimately become transformed into a lithopedion and the patient will carry this burden with her to the grave. There is one such case in my series where this literally happened.

CASE 5.—This was a Chinese woman of 58. Little is known of this patient, as she was never able to give her history. She was admitted to the hospital in a state of unconsciousness on Aug. 28, 1946. A diagnosis of cerebral hemorrhage was made and the patient never regained consciousness before her death a few days later. A stony hard mass was present in the abdomen, reaching up to just above the level of the umbilicus. It was said to have been there for over 20 years. X-ray examination showed a beautiful example of lithokelyphopedion, as shown in Fig. 5. Unfortunately no autopsy was obtainable.

With regard to menstruation it is interesting to note that, after a variable interval of time, normal menstruation tends to become re-established even though the patient is still carrying an extrauterine fetus. This happened in 5 of my cases, the menses reappearing at 40, 44, 56, 58, and 59 weeks, respectively, after the onset of amenorrhea, and thereafter continuing regularly until operation was carried out. In no case of my series did normal intrauterine pregnancy supervene, although the literature abounds in reports of patients who had anything from one to seven normal pregnancies, while still carrying the extrauterine fetus.

Diagnosis.—Diagnosis depends essentially upon first recognizing that the patient is pregnant and, second, establishing the fact that the pregnancy is extrauterine. The fact that the diagnosis in these cases is often puzzling is due, more often than not, to a failure to think of the presence of the two possibilities which I have just mentioned, rather than to any inherent difficulties in the condition.

On physical examination one is often struck by the abnormal position of the child. In my series of cases there were 4 transverse presentations, 4 breech presentations, and only 2 vertex presentations (I have excluded the lithopedion and the "bag of bones" from these figures). And not only is the incidence of abnormal presentation very great, but the position of the child is often unusually high in relation to the pelvic brim. Furthermore, the at-

titude of the child is frequently abnormal, there being a tendency to extension in an abdominal pregnancy and to hyperflexion and compression in an intraligamentous pregnancy. The fetal heart tones were unusually clearly heard in the one case where we were able to demonstrate a living baby before operative treatment was undertaken.

Uterine contractions of the Braxton Hicks type will not be felt in these cases. I have not had occasion to employ the Pitocin or the Pituitrin test in order to differentiate between an intrauterine and an extrauterine pregnancy, and would rather question its advisability and safety.

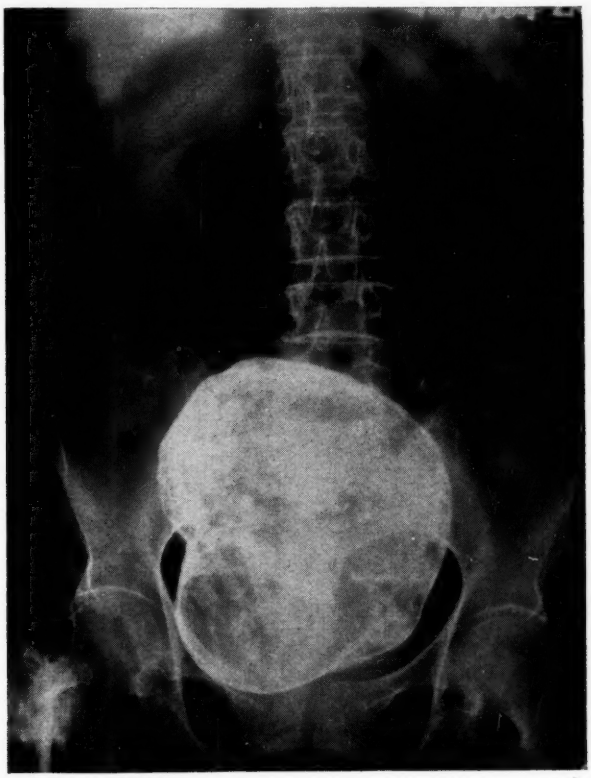

Fig. 5.—A beautiful example of lithokelyphopedion of 20 years' duration.

Radiological examination is unquestionably the most useful diagnostic aid which we possess and was carried out on all of our cases. A plain film will often suggest the diagnosis by demonstrating a fetus in an abnormal position or attitude, as well as by showing an abnormally thin soft-tissue covering in place of a uterine shadow of normal thickness. The failure of the fetus to change position in successive examinations is also suggestive of extrauterine pregnancy. I regret to state, however, that in 3 of my cases an x-ray examination failed to suggest that the pregnancy was extrauterine. In Case 2 (already mentioned), the presentation appeared to be a normal vertex one, and it was only after the failure of induction that the true state of affairs was diagnosed. In Case 3, the fetus was known to be dead and induction in another hospital

was known to have failed, but the x-ray showed a fetus presenting as a breech, with a marked Spalding sign, and the extrauterine nature of the condition was not diagnosed until a further attempt at surgical induction was made. In the remaining case (No. 4), which will be mentioned again later, the clinical and radiological findings seemed to point toward a diagnosis of placenta previa. The later course of the case indeed showed that the placenta was interposed between the presenting part and the cervix, but it was completely extrauterine in its situation and not intrauterine.

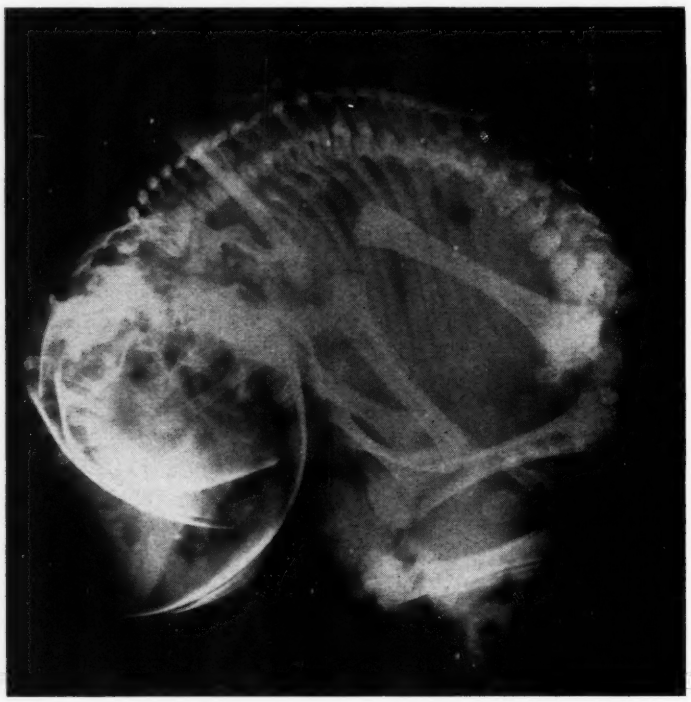

Fig. 6.—X-ray film of extrauterine fetal sac with its contents after removal. Note the exaggerated Spalding sign as well as the "ball" sign, also the diffuse spread of calcification throughout the body but not in the wall of the sac.

Other significant findings that may be demonstrated by x-ray examination are those showing the death of the fetus and the subsequent changes that may take place in the fetus and its sac. A very clear Spalding's sign was found in several of my cases. In others the so-called "ball" sign was found, with hyperflexion of the fetal spine and compression of the whole fetal skeleton into a rounded mass. Fig. 6, taken after removal of a secondary abdominal pregnancy in Case 6, shows this sign very well. In cases where infection of the gestation sac has taken place, with disintegration and skeletonization of the fetus, the bones will be seen as an indiscriminate mass piled together without any order. Finally, in the more advanced cases, areas of calcification may be seen in the soft parts of the fetus as well as in the placenta and membranes and all stages up to the fully developed lithopedion may be found (Fig. 5).

But the absolute diagnosis of advanced extrauterine pregnancy depends upon hysterosalpingography and the demonstration of fetal skeletal parts lying outside the normal uterine cavity. In a fair proportion of cases the tubes may also be visualized and there may be a clear indication as to the side on which the extrauterine pregnancy has developed. There are not many reports on this type of examination, but Osborn, Greenhill, and Friedman, among others, have published interesting examples. Hysterosalpingography

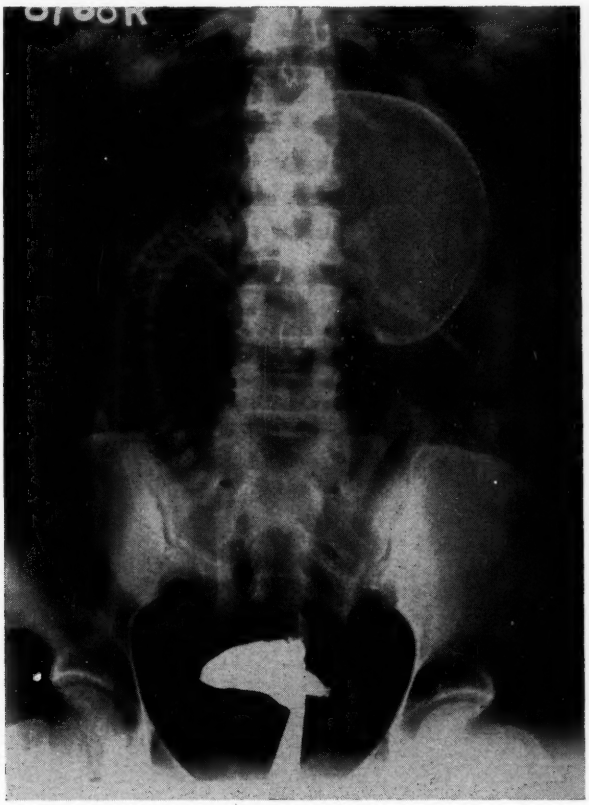

Fig. 7.—Hysterosalpinogram showing relationship of uterine cavity to fetus. Outline of left tube leads to fetal sac.

was carried out on 6 of my cases and in each instance enabled a correct diagnosis to be made. Fig. 7, taken from Case 8, shows a good example of an extrauterine fetus presenting by the breech, and its relation to the uterine cavity. The fine outline of the left tube can be traced going in the direction of the fetal sac, with which it proved to be connected. The opaque globules seen projecting from the left side of the uterus lower down proved at operation to be contained within the right tube, which was in a state of mild hydrosalpinx and adherent behind the uterus. Fig. 8, taken from Case 11, shows an interesting condition of adhesive endometritis, as evidenced by the irregular filling of the endometrial cavity, which is seen against the confused background of fetal skeletal parts situated outside the uterus.

Biological tests for pregnancy have not been found of very much value in diagnosis, although they were carried out in a number of the cases. In advanced cases where the fetus has been dead for weeks or months the test is invariably negative. In cases where the patient is seen while the fetus is still living and viable the test is, of course, positive, but one tends to place more weight upon such positive findings as the presence of fetal movements and the auscultation of the fetal heart under such circumstances. Hudnall Ware made the interesting observation that, in two cases in which the babies were alive at the

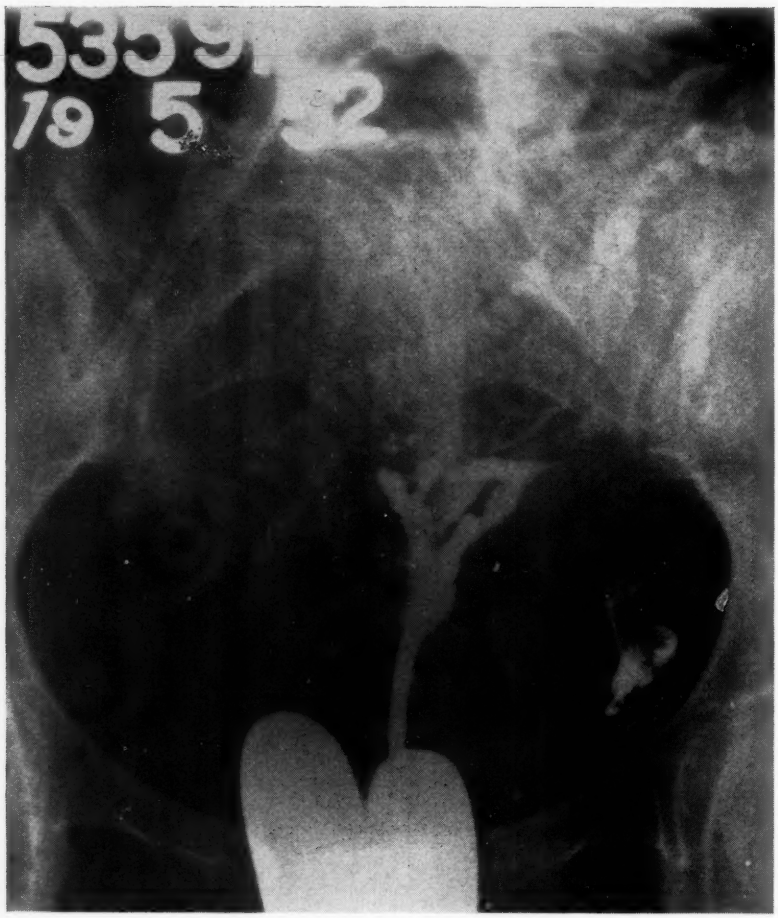

Fig. 8.—The uterine cavity is outlined against a confused background of extrauterine fetal bones. The irregular filling of the cavity is due to adhesive endometritis.

time of the operation and the placenta was left in situ, positive Friedman tests were obtained on specimens of urine from the patients for 35 and 47 days after operation, respectively. I regret that it did not occur to me to do likewise in a similar case of my own.

The differential diagnosis of advanced extrauterine pregnancy includes a large number of intra-abdominal conditions. Undoubtedly the most common mistake is to confuse it with normal pregnancy or with intrauterine death of

the fetus followed by missed labor. In any case of persistent malpresentation extrauterine pregnancy should be considered. Next would come conditions such as ovarian cysts or fibroid tumors complicating pregnancy. Then would come placenta previa, premature separation of the placenta, and a host of other conditions, not omitting intestinal complications. The original diagnoses in the 12 cases belonging to this series are shown in Table III.

TABLE III. ORIGINAL DIAGNOSES IN 12 CASES OF ADVANCED EXTRAUTERINE PREGNANCY

Advanced extrauterine pregnancy	7
Intrauterine death of the fetus with missed labor	2
Normal pregnancy at term	1
Placenta previa	1
Ovarian tumor	1
Total	12

In 3 of these cases where the original diagnosis was wrong the correct diagnosis was reached before operation, leaving 2 cases where the true diagnosis was made only at operation.

Treatment.—There is no doubt that the correct treatment of this condition is to carry out a laparotomy as soon as the diagnosis is made, with the possible exception of certain cases nearing term, where the delay of a few weeks may result in a living baby. Beck, who has already been quoted, regards the thirty-eighth week as the optimum time for operation in these cases and I am in agreement with him that the chances of obtaining a normal living baby are such that it is not justifiable to disregard the interests of the child. It is unquestionably a mistake to wait for the death of the child in the hope that the diminished placental circulation will render operation easier. Complications, such as maceration of the fetus and possible infection of the sac, may actually make the whole operation far more hazardous to the patient. The actual details of operative treatment will vary with each individual case, but in general the aim is to remove the gestation sac, complete with fetus and placenta, if this is possible. It may be necessary to remove the fetus and placenta separately and to leave portions of the sac behind. Or it may be necessary to leave the placenta behind if its removal appears to carry with it too great a risk of hemorrhage. Marsupialization and drainage, formerly widely used in these cases, are now seldom necessary, except in cases such as No. 1 of this series, where gross infection of the gestation sac had taken place, with distintegration of the fetus and the establishment of a fistulous connection with the bowel. Experience with operations in these cases has shown that the majority of them conform to a certain broad pattern. On opening the abdomen a certain number of adhesions betwen the sac and the omentum and abdominal wall are likely to be encountered. After these have been separated it is generally possible to identify the fundus of the uterus and the appendages, and to gain an impression as to the side from which the pregnancy has arisen. Generally the pregnancy will be found to have originated from a tubal pregnancy which has ruptured either into the peritoneal cavity to form a secondary abdominal pregnancy, or into the broad ligament to form an intraligamentous pregnancy.

The next step in the operation is to separate all adhesions between the sac and the other abdominal structures, particularly the transverse, descending, and sigmoid colon. It is most important to preserve the blood supply of the colon and special care should be taken in separating the transverse mesocolon and the pelvic mesocolon, and it may be necessary to allow a little of the outer layer of the gestation sac to remain on these structures, rather than risk injury to the colic vessels by too close a removal. Following this the sac is attached only to the pelvic structures, and by dividing the peritoneum of the broad ligament above and parallel to the round ligament on the side from which the pregnancy springs, it is usually possible to enucleate the entire mass, with or without the uterus, after clamping and dividing the usual vascular pedicles.

Operation was carried out in 11 of my 12 cases, the only patient not operated upon being the woman of 58 years of age with a lithopedion of 20 years' standing who was admitted to hospital with a fatal cerebral hemorrhage. An analysis of the operative procedures which were carried out is given in Table IV.

TABLE IV. ANALYSIS OF OPERATIVE PROCEDURES IN 11 CASES

Removal of complete gestation sac with fetus and placenta	6
Removal of complete gestation sac with fetus, placenta, and uterus	3
Removal of living child, placenta left behind	1
Removal of skeletonized fetus, marsupialization of sac	1
Total	11

A word may be added as to the treatment of the placenta, which Lawson Tait (in 1888) described as "the crux of the discussion." There is no doubt that complete removal of the placenta, if it can be accomplished without undue danger to the patient, is the ideal procedure, and this can usually be achieved if the vascular supply can be reliably controlled. In the event of the placenta being so implanted that its removal would be accompanied by dangerous or fatal hemorrhage it is unquestionably safer to leave it behind and to close the abdomen than to institute such measures as marsupialization or drainage. These facts were recognized by Lawson Tait in his day, and were very clearly restated by Alfred C. Beck in 1919 in his classical contribution to this subject. In only one of my patients was it necessary to leave the placenta in situ, but I am convinced that any attempt to remove it in this case would have caused fatal bleeding. The subsequent history in this case was of interest because, while the patient never experienced any troublesome aftereffects, it took 3½ years before the placenta completely disappeared and was no longer palpable on bimanual examination. I had been led to expect, after reading the accounts of the rapid absorption of placental tissue when placed in the peritoneal cavity of a dog, that absorption would be complete within a few months. I have been interested to learn that other workers have had the same experience.

Types of Pregnancy.—The types of pregnancy found at operation were as given in Table V.

In all 5 of the secondary abdominal cases there was evidence that during the earlier stages of the pregnancy rupture of a primary tubal pregnancy had

occurred. Fig. 9 shows the condition found after operation in Case 11. The specimen consisted of the uterus with both appendages and the gestation sac. The total weight was 2 pounds, 12 ounces. The uterus measured 9 by 7 by 3.5 cm. and was of uniform size and normal consistency. On opening the cavity the endometrium of the anterior and posterior surface was found to be adherent in several places. The right appendage was in a state of chronic salpingo-oophoritis. The fimbriated end of the tube was widely adherent to the ovary, but was patent to a probe. The lumen of the isthmic and interstitial portion was obliterated. The left tube was elongated and patent in its interstitial and isthmic portions. The ampulla was dilated to form a cup-shaped sac measuring 6.5 by 5.5 cm., expanding at its outer end to fuse with the gestation sac. The gestation sac measured 15.5 by 10 cm. It contained the remains of a fetus which had apparently reached term. There was no fluid in the sac. There was focal calcification of the wall which was about 0.2 cm. thick and densely adherent to the fetus. The ovary could be clearly identified behind, connected with the uterus by the ovarian ligament medially and blending with the sac laterally. The placenta was identified as a thickened, partly calcified area lying between the fetus and the extremity of the left tube, forming part of the wall of the sac in this place.

TABLE V. ELEVEN CASES OF ADVANCED EXTRAUTERINE GESTATION

Secondary abdominal	5
Intraligamentous	4
Tubal, unruptured	1
Interstitial, unruptured	1
Total	11

There were 4 intraligamentous pregnancies and in 2 of them there was a clear history of rupture into the broad ligament in the early weeks. Fig. 10 shows a typical example of such a pregnancy which was removed from Case 8. The specimen consisted of a male fetus and placenta in a sac, weighing altogether 6½ pounds (without the contained fluid). The fetus weighed 4 pounds and showed no gross external anatomical malformation, apart from some constriction of the left ankle by the cord. The umbilical cord was 24 cm. in length and was twisted once around the left leg tightly and inserted eccentrically into the placenta. The placenta weighed 2 pounds and measured 20 by 14 by 4 cm. The maternal surface was adherent to the membranelike inner surface of the sac over the area which was buried between the layers of the broad ligament.

Case 9 provided an interesting example of an enormous unruptured dilatation of the whole of the left tube. The specimen as removed at operation is shown in Figs. 11 and 12. At operation it was noted that the left broad ligament was not dilated and the ovary was lying flattened out and closely applied to the lower aspect of the tube. The uterus was lying almost horizontally with the fundus pointing to the right. The right tube was normal and patent and the right ovary was normal. The entire tube was easily removed with little or no hemorrhage, and pathological examination of the specimen

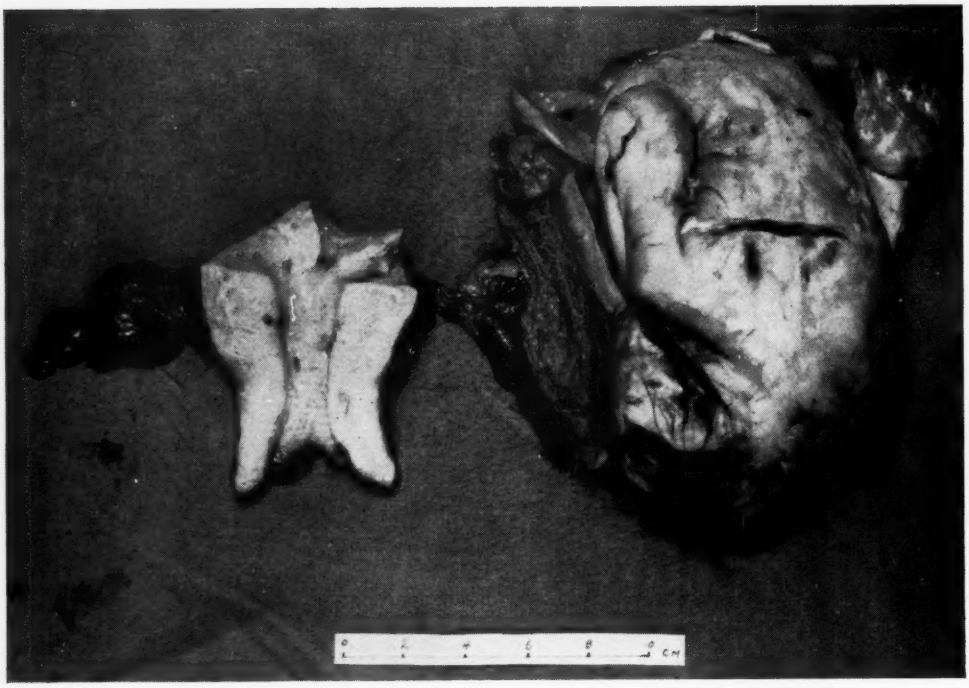

Fig. 9.—Abdominal pregnancy as removed at operation (for description see text).

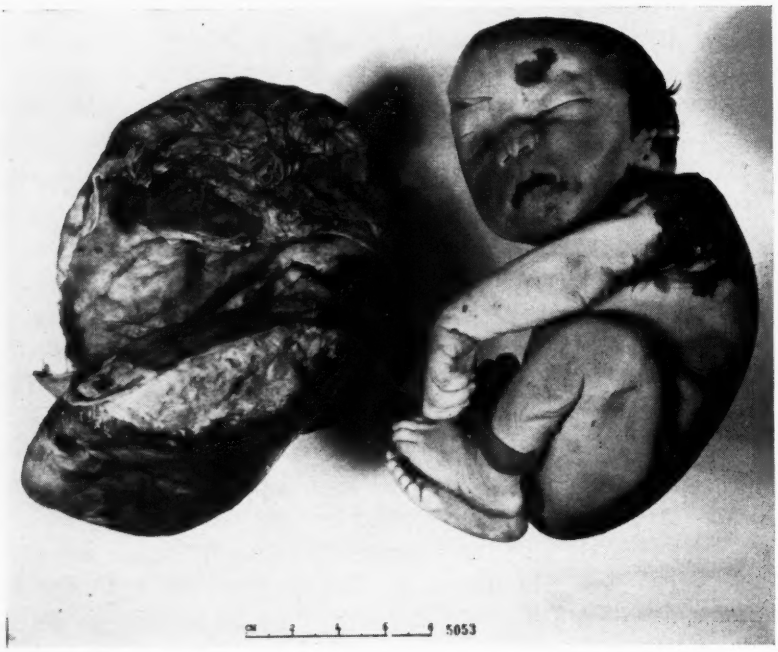

Fig. 10.—Intraligamentous pregnancy as removed at operation (for description see text).

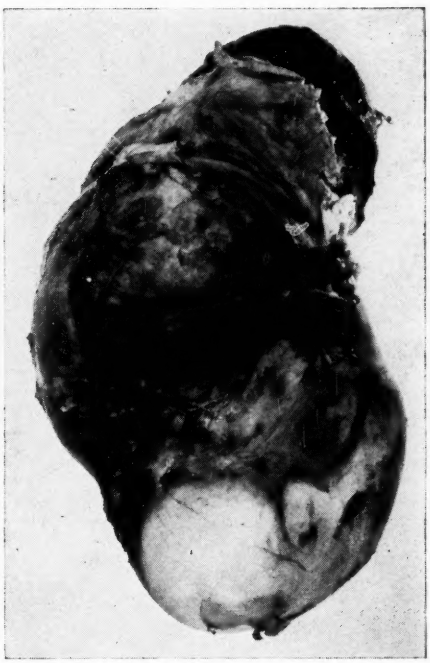

Fig. 11.—Unruptured tubal pregnancy as removed at operation.

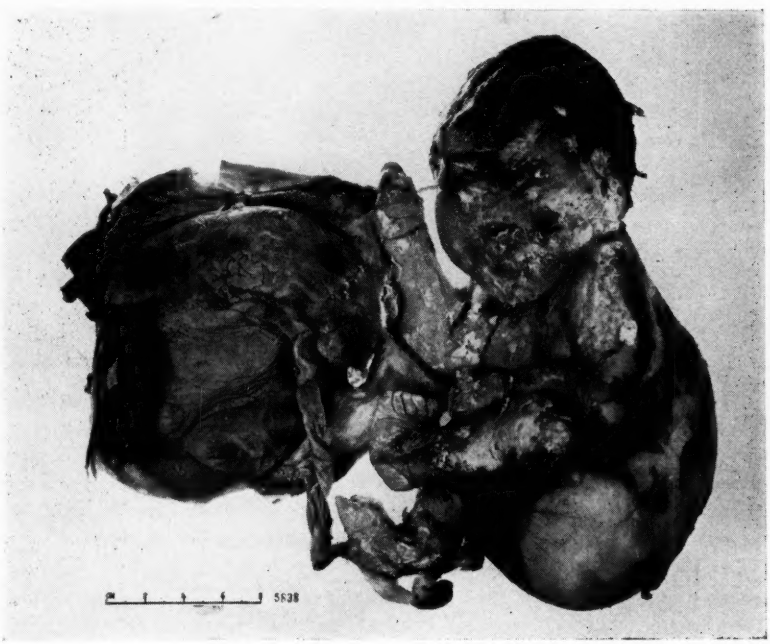

Fig. 12.—Contents of specimen shown in Fig. 11 after opening.

showed that it consisted of a large oval mass weighing 6 pounds, 12 ounces, and measuring 30 by 16 cm. At the lower pole of the mass the wall of the sac was very thin and the head of the fetus could be seen protruding. Microscopical examination of the wall of the sac showed that it contained a small amount of smooth muscle and abundant collagen fibrils. No ovarian tissue was seen.

Perhaps the most interesting condition that was found was an unruptured interstitial pregnancy in Case 7.

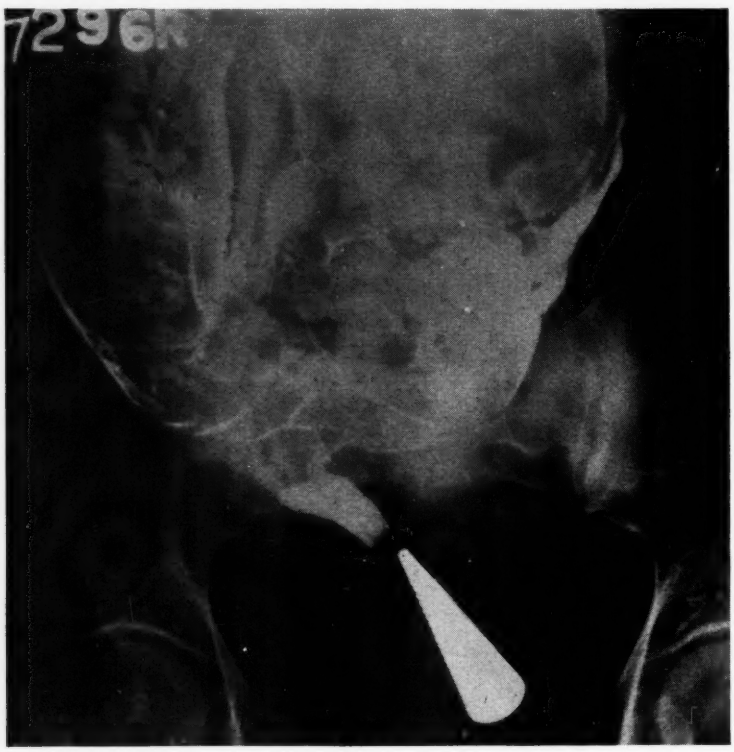

Fig. 13.—Hysterosalpingogram in case of unruptured interstitial pregnancy. The uterine cavity communicates above and on the left side with a huge space in which an interstitial pregnancy is situated.

This patient did not present herself for treatment until the pregnancy had reached a duration of 69 weeks. After the onset of amenorrhea the patient complained only of progressive abdominal enlargement, with very mild abdominal pain. She never felt any fetal movements. At term there was a history of severe abdominal pain following which the abdomen grew smaller, and at the fifty-sixth week a large amount of fluid escaped from the vagina. Menstruation returned at the sixtieth week and the patient had 3 normal periods before she came for examination. The abdomen contained a firm rounded mass of uneven consistency reaching a point 24 cm. above the symphysis. Mobility was fairly free. The hysterosalpingogram (Fig. 13) gave a very unusual picture, which showed an apparently normal uterine cavity and widely outlined the limits of the fetal membranes. Intrauterine death of the fetus was diagnosed, but as medical induction with the estrogen-Pitocin method failed, laparotomy was performed. Operation revealed that an unruptured interstitial pregnancy was present on the left side. There were numerous adhesions to the omentum and intestines, but after these had been separated it was found that the left cornu of the uterus was

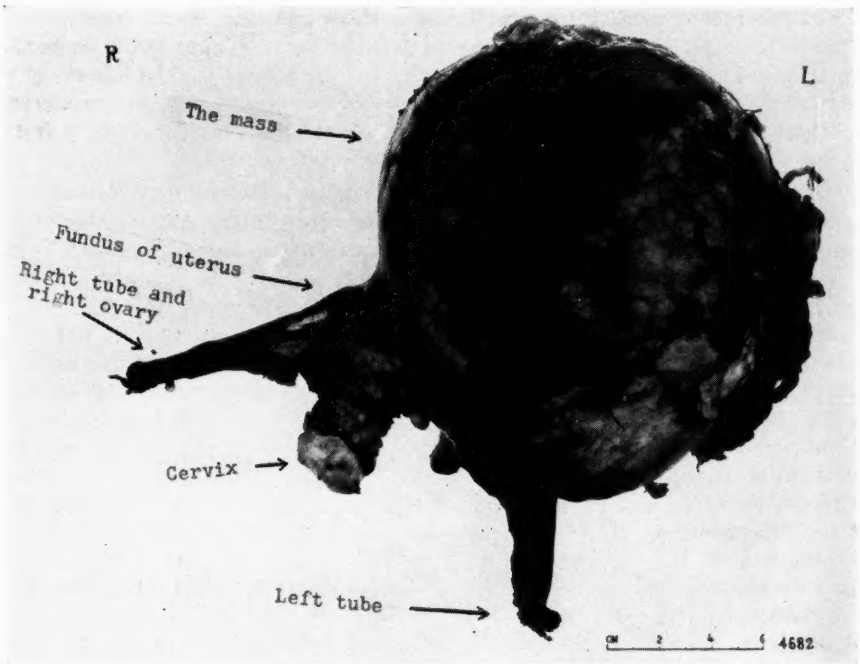

Fig. 14.—Specimen of unruptured interstitial pregnancy (for description see text).

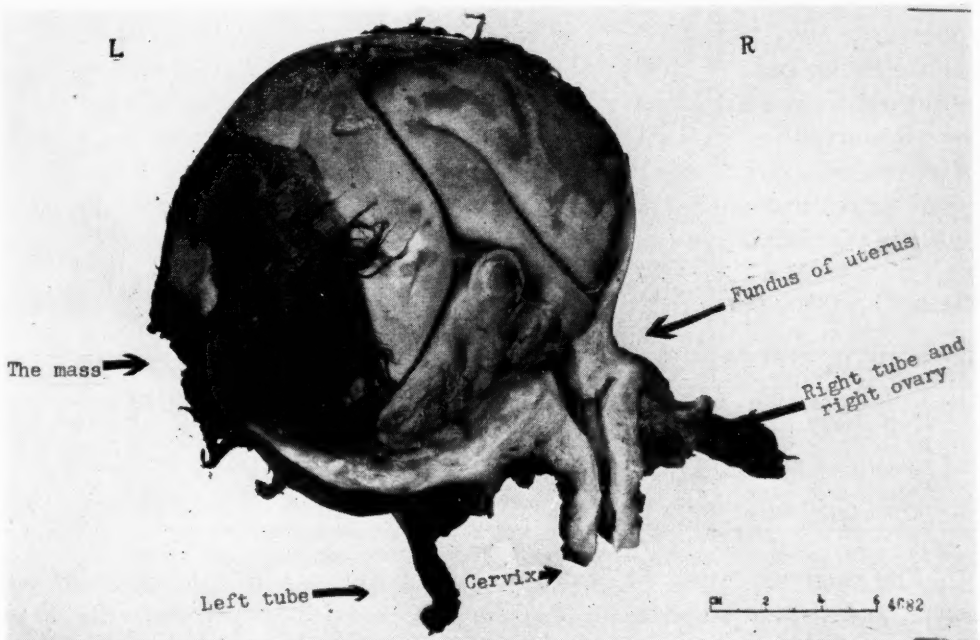

Fig. 15.—Unruptured interstitial pregnancy, opened from the rear to show relationships (see text).

enormously expanded. The right tube and ovary, together with the right round ligament, preserved their normal relationship to the uterus. On the left side, however, a little more than one-half of the fundus was incorporated in the swelling and there was a considerable separation between the round ligament (which entered the mass near its lower and inner borders) and the left tube (which was attached to the mass rather far laterally. The left ovary was situated posteriorly at a point not very far distant from the uterus. The entire uterus was removed, together with both tubes and ovaries. The patient made a good recovery from the operation and was discharged well on the seventeenth day after operation.

Pathological examination of the specimen (Fig. 14) showed that it consisted of the uterus, two tubes, and two ovaries; there was an enormous enlargement of the left cornu of the uterus. The specimen weighed 4 pounds, 5 ounces. The distance from the right cornu to the cervix was 9 cm. The measurements of the left cornual enlargement were 15 by 18 by 10.5 cm. The length of the right tube was 9 cm. and the left tube measured 8 cm. from the point of its attachment at the lower pole of the swelling to its free extremity. The right ovary measured 2.5 by 1.5 by 7 cm. The left ovary was attached to the swelling by a ligament measuring 3.0 by 3.0 by 0.3 cm. On removal of a strip of the posterior wall of the sac (as seen in Fig. 15) a fetus measuring 15 by 13 cm. was found to be curled up inside the dilated interstitial portion of the left horn of the uterus. At the lower end the wall was 1.5 cm. in thickness, but at the upper part of the sac the wall measured only 3 mm. in thickness. Microscopically the sac wall consisted of hyalinized connective tissue with a few blood vessels and a very few muscle fibers. No endometrium was found. The uterine cavity, however, showed mild hyperplasia of the endometrium, with no sign of any decidual reaction. Interstitial pregnancy usually results in rupture with severe hemorrhage at a later date than with other forms of tubal pregnancy, but rarely later than the sixth month (Litzenberg). This case was remarkable in that it proceeded to term without hemorrhage or rupture. The spontaneous escape of the liquor through the cervix 13 months after the commencement of the amenorrhea led to the assumption that the pregnancy was intrauterine and that the condition was one of missed labor. A more critical interpretation of the hysterosalpingogram, however, might have led to the correct diagnosis.

Results.—The results of treatment of these cases, as far as the mother is concerned, have become progressively better over the years, as is shown by the following comparative table of some of the larger series of reported cases subjected to operation. At the same time it must be confessed that the reported mortalities are still very formidable and that the results of treatment of advanced extrauterine pregnancy cannot be compared with those of ruptured ectopic pregnancy in the early months, where the accepted mortality today is approximately 1 per cent.

TABLE VI. COMPARATIVE RESULTS OF OPERATIVE TREATMENT OF ADVANCED EXTRAUTERINE PREGNANCY, 1809 TO 1946

AUTHORS	CASES	YEARS	MATERNAL MORTALITY
J. S. Parry	62	Prior to 1876	51.61%
H. A. Kelly	77	1809 to 1896	57.3 %
P. B. Bland	240	1813 to 1907	34.7 %
Hellman and Simon	316	1809 to 1933	31.9 %
Cornell and Lash	236	1919 to 1932	14.3 %
H. Hudnall Ware	249	1933 to 1946	14.85%

The common causes of death have always been shock, hemorrhage, and sepsis, and at least 80 per cent of all the reported deaths have been due to one or other of these causes. There is no doubt that the introduction of chemotherapy and of antibiotics and the more extended use of blood transfusion have

done more than anything else to bring down the mortality from this condition, and it must be remembered that the mortality figures shown in the table do not adequately reflect these advantages.

In my own series of 11 operations there was no mortality. This I ascribe very largely to the fact that all but 2 of these cases were handled since the introduction of chemotherapy and that adequate blood transfusion facilities were available for all of them.

My results, so far as the child is concerned, are far less encouraging. In the whole series there has been only one living baby. In other reported series to which reference has already been made, there has been a far higher incidence of infant survival. In my own cases, however, the pregnancy had progressed beyond the forty-second week in 10 out of the 12 patients, and fetal death had occurred long before they sought treatment. In one other case the fetal heartbeat had only just disappeared when the patient was referred for treatment and the child might have been saved if the mother had come a few hours earlier. In the one remaining instance a living baby was obtained, and perhaps I may be pardoned if I conclude my address to you this evening by telling you the story of this case.

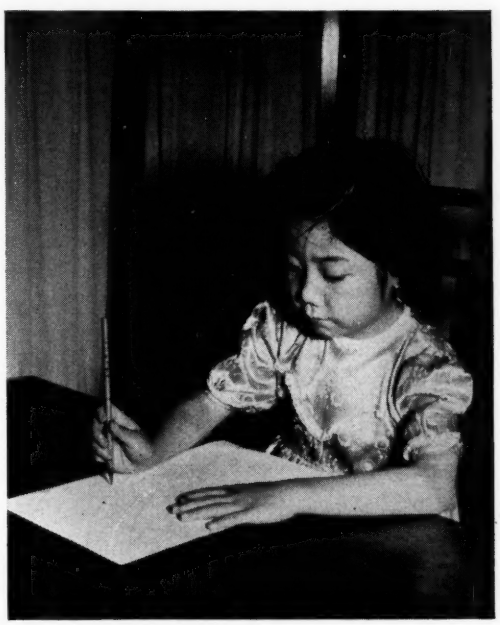

Fig. 16.—Child aged 6½ years, who survived operation for advanced extrauterine pregnancy. There were no deformities.

The patient, a Chinese married woman of 39 years of age, was admitted to hospital on Sept. 5, 1946, during the thirty-sixth week of her pregnancy, on account of increasing abdominal discomfort and malpresentation. She had one child aged 19 and a history of gonococcal infection 10 years previously. Her last menstrual period was Dec. 24, 1945. During the eighth week of the pregnancy she experienced severe lower abdominal pain for two hours, but no vaginal bleeding. The acute pain passed off, but the patient had frequent attacks of milder pain in the lower abdomen throughout the remainder of her pregnancy, and from the thirty-second week onward the pain became continuous.

On examination the abdomen was rather tense and the fetus was lying transversely in a very high position with the head to the right and the breech to the left. The fetal heartbeat was very clearly heard. Vaginal examination revealed a soft swelling filling the right side of the pelvis, with pulsation in the right fornix. X-ray examination confirmed the transverse lie and the unusually high situation of the whole fetus was commented upon.

A diagnosis of placenta previa was made, and the patient was kept in hospital awaiting the onset of labor, as cesarean section was thought to be advisable.

On the morning of September 28 (3 days before term) the patient had a sudden attack of acute abdominal pain. The abdomen was found to be completely rigid everywhere, and it was impossible to feel any fetal parts, although the fetal heart was still clearly audible. The patient's pulse had risen from 76 to 110, and there was no fever but a considerable degree of shock. There was no vaginal bleeding, but abruptio placentae with extensive concealed hemorrhage was suspected.

At operation, which was carried out immediately, the peritoneal cavity was found to be flooded with amniotic fluid and a living female baby was seen floating about amid the coils of intestine. The child was rapidly delivered and the cord was tied and severed. Respiration was spontaneous and the child cried well. Further examination of the abdominal cavity showed that the pregnancy had been situated within the right broad ligament and that the thin sac consisting of amnion, chorion, and peritoneum had ruptured near its summit. The placenta, which was of normal size, was situated in the base of the broad ligament and the anterior and posterior peritoneal folds had been pushed widely apart so that the placenta was implanted over the bifurcation of the right common iliac artery and extended deeply into the pelvis filling the right vaginal fornix and pushing the uterus over to the left side. It was obvious that any attempt to remove the placenta would result almost certainly in uncontrollable hemorrhage. It was therefore decided to leave the placenta in situ. The cord was ligated with catgut and divided at its placental attachment. Its total length was 65 cm. The membranes were also trimmed down close to the placental edge, and the placenta was then left undisturbed at its site of implantation with its amniotic surface facing upward into the abdomen. There was practically no bleeding during any part of the operation.

The patient made an uninterrupted recovery and was discharged well on the twentieth day after the operation. The placenta was still palpable at this time as a firm, fixed, painless mass situated over the brim of the pelvis on the right side and extending downward into the pelvic cavity. This mass did not completely disappear until 3½ years later. Both mother and child are alive and well today.

The baby was a perfectly normal female child who weighed 3,100 grams at birth and measured 47 cm. in length. No malformations of any sort were present, and the baby thrived well on breast feeding. The child has been followed for nearly 7 years now, and has proved to be an unusually promising child for her age. She took second place in her class at school and is in every sense a normal and intelligent little girl, as her photograph demonstrates (Fig. 16).

While I was not able to diagnose this case correctly before operation, it has brought me greater satisfaction than any of the other cases I have mentioned because of its doubly successful outcome.

I would like to acknowledge the help and encouragement which I have received from many colleagues during the years that have elapsed since my interest was first aroused in this subject, and in particular to express my thanks to Drs. F. J. Farr and H. C. Ho for some beautiful roentgenograms and to Professor P. C. Hou for pathological examinations and the generous assistance of his photographic department.

CARDIOVASCULAR PHYSIOLOGY IN NORMAL PREGNANCY: STUDIES WITH THE DYE DILUTION TECHNIQUE*

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ALTHOUGH considerable investigation of the hemodynamics during pregnancy has been done by Stander and Cadden,[31] Thomson and associates,[34] Tysoe and Lowenstein,[35] Hamilton,[12] and Werkö and co-workers,[38] it remains a subject poorly understood. That there has been considerable dispute as to the nature and magnitude of the hemodynamic changes during pregnancy is unquestionable. Therefore, we consider it timely that a study of this nature should be made. It is obvious that the normal physiology during pregnancy must be determined before a study of the pathological changes would have any significance. We have undertaken in this study to establish the cardiovascular physiology during normal pregnancy reserving the physiology during abnormal pregnancy for future studies. The techniques used are entirely new and, to my knowledge, have never before been applied in a detailed study during pregnancy.

Cardiac Output

The cardiac output, a functional measure of cardiac activity, may be defined as the amount of blood expelled by the left ventricle into the aorta in a unit of time. The cardiac output is usually expressed as liters per minute; however, in nonpregnant individuals the body size and weight may be taken into consideration. The cardiac output may then be expressed as cubic centimeters per minute per kilogram, or as the cardiac index, i.e., liters per minute per square meter of body surface. As will be explained later a false impression is created if body size and weight are considered in a discussion of hemodynamics in pregnancy.

The stroke volume is the amount of blood expelled by the left ventricle with each contraction. This may be obtained by dividing the minute volume by the heart rate per minute.

Under fixed environmental and physiological conditions the cardiac output is constant and reproducible. It is most constant at basal conditions and is said to be proportional to the surface area. The cardiac output will vary depending upon the influence of various extraneous factors. Factors that will cause an increase in cardiac output include the ingestion of food or fluids, exercise, anxiety, anemia, anoxia, an increase of body temperature and

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thyrotoxicosis. A decrease in cardiac output may be produced by myxedema, shock, and congestive heart failure. An individual may have severe cardiac disease and still have no alteration of cardiac output unless decompensation occurs.

The cardiac output may be varied by an alteration of the pulse rate, of the degree of diastolic filling, or of the strength of systolic discharge of the ventricles. Therefore, it is obvious that the output per minute may vary considerably even though the pulse rate remains relatively constant. During pregnancy the variation of the cardiac output is primarily produced by an alteration of the degree of diastolic filling of the ventricles. This may be done by an alteration of the venous return to the heart or by an alteration of the length of diastole. A greater diastolic filling leads to a stronger contraction and a greater stroke volume.

The regulation and control of the cardiac output are chiefly reflex through the vagus and cardiac sympathetic nerves. From the cardiac centers in the midbrain a continuous flow of impulses tends to regulate the action of the heart depending upon the need of the individual at that particular time. The pressor reflexes, being the most important, act in hypotensive states to elevate the blood pressure. The needs of the tissues at the periphery tend to regulate the action of the heart. Greater demands for oxygen are accompanied by an increase in cardiac output. Therefore, it is apparent that the output may vary considerably within a few minutes depending upon the influence. Pregnancy is accompanied by an increase in the oxygen consumption which might be expected to cause a rise in cardiac output. Actually the observed increases are greater than the increases in metabolism.

Lindhard[24] (1915), Liljestrand and Stenström[23] (1926) and Gammeltoft[6] (1926) were the first to determine the cardiac output during pregnancy. They applied the nitrous oxide method of Krogh and Lindhard. Stander and Cadden[31] in 1932, using the acetylene technique of Grollman, found a cardiac output of 2.2 L. per minute per square meter of body surface in nonpregnant females with an increase of 60 per cent at term. Despite the limited number of observations and the inaccuracies of the methods used, these investigators published results that were fairly consistent.

More recently it has been realized that the earlier methods contained serious errors and that an application of more reliable methods was necessary. Werkö, Bucht, Lagerlöf, and Holmgren[37] in 1948 and Werkö, Lagerlöf, Bucht, and Holmgren[38] in 1950, using the Fick method, found an increase of from 1.0 to 1.6 L. per minute during pregnancy, with a decrease during the last few weeks. Hilary Hamilton,[12] in 1949, using the Fick principle, reported 4.5 L. per minute for nonpregnant women with an increase during pregnancy to a maximum of 5.73 L. per minute at 30 weeks' gestation and a decrease from this point to term.

Among the numerous methods that have been devised for the determination of cardiac output there are only two in which no empiric constants are used. These two, the Fick principle and the dilution technique, are probably

the most accurate in use today. The foreign gas techniques of Krogh and Lindhard, Grollman, Henderson and Haggard,[18] and others not only require difficult gas analyses but also depend upon the solubility and diffusibility of the individual gases.

In 1897 Stewart,[32] using sodium chloride, showed that the cardiac output could be calculated from the dilution of a known amount of injected substance by the blood which passes through the heart during a known period of time. Gross and Mittermaier[11] in 1926 suggested the use of dye substances as suitable for injection and colorimetric determination. All of the investigation up until this time had been done in dogs. This method was not applied to man until 1928.

Hamilton, Moore, Kinsman, and Spurling[13] in 1928 adapted the Stewart principle and developed an accurate method for the determination of the cardiac output in man. They considered that the older methods were inaccurate because there was no way of knowing when recirculation had occurred. Hamilton and his associates pointed out that when dye is injected into the venous system and a series of arterial blood samples are rapidly taken the dye concentrations of the samples form a definite curve when expressed against time in seconds on semilogarithmic paper. It has been shown by numerous experiments on models and heart-lung preparations by Kinsman, Moore, and Hamilton[21] that the relationship between the logarithm of the concentration and time forms a straight line on the descending slope of the primary circulation curve. Therefore, the descending slope may be extrapolated to the base line as if no recirculation had occurred. This shows the curve of primary circulation and serves to differentiate the once-circulated dye from the twice-circulated dye. Newman and collaborators[27] state that curves obtained from a mechanical model are nearly identical with the theoretically derived curves. The object of the procedure is to determine the degree to which the injected substance has been diluted by the blood passing through the heart and lungs during the time of the primary circulation. The cardiac output is calculated from the amount of blood which has diluted the known amount of injected substance over a known period of time.

Hamilton's principle and theory were good but his earlier methods contained serious errors. Phenoltetraiodophthalein was first used by Hamilton, but later was proved unsatisfactory due to diffusibility and hemolysis.

The Hamilton dye dilution principle has been compared with the Fick principle by many investigators. The first comparison was made in 1929 by Moore, Kinsman, Hamilton, and Spurling.[25] They concluded that the injection method was equal in accuracy to the Fick method and that the average difference between the two was 4.7 per cent. This comparison was repeated in 1948 by Hamilton and others.[16] They obtained 6.6 L. per minute with the Fick method and 6.8 L. per minute with the injection method. Werkö, Lagerlöf, Bucht, Wehle, and Holmgren[39] in 1949 made a comparative study between the two methods and found that there was no significant difference. Wiggers[40] pointed out that the dilution method was at least as accurate as the Fick method.

In a comparison between the dye method and radioactive methods Lawson, Cantrell, Shaw, Blackburn, and Adams[22] found that the two compared within 7 per cent. Hamilton and Remington[15] found the error in the dye technique to be plus or minus 10 per cent.

The advantages of the dye technique over the Fick procedure are numerous. The dye-injection technique is a shorter procedure, requires much less equipment, produces less anxiety and apprehension in the patient, and is technically easier. In the Fick procedure the blood must be collected under oil, the gas determinations are laborious and the experimental error is as much as with the dye method. A mixed venous blood sample must be collected and this is difficult even with cardiac catheterization. Warren, Stead, and Brannon[36] have stated that "the catheter method is a useful procedure, but errors are sufficiently large so that the values in one set of determinations may not represent the actual cardiac output." The cardiac output as measured by the Fick technique represents the output over a period of eight to ten minutes. However, when it is measured by the dye technique the output is over a period of less than a minute. This means that rapid changes in cardiac output may be measured by repeated determinations. The entire procedure of dye injection and sample collection requires only six minutes and repeated determinations can be made on the same patient with no discomfort. The only serious objection to the dye procedure is that the calculations are perhaps somewhat more involved than those of the Fick procedure.

Blood and Plasma Volume

It is generally considered that the plasma and blood volumes are increased during pregnancy. There is perhaps some disagreement as to the degree of increase and whether there is a decrease during the last month of pregnancy corresponding to the reported decrease in cardiac output.

In 1915 Keith, Rowntree, and Geraghty[20] pointed out that the plasma volume could be calculated from the dilution of a dye substance (vital red) by the blood stream. In 1920 Dawson, Evans, and Whipple[4] further utilized this dye dilution principle but found that Evans blue dye (T-1824) was superior as a dye substance. Gibson and Evans[7] in 1937 made several refinements in previous techniques and published the first clinical blood volume studies. Gregersen, Gibson, and Stead[9] pointed out that the spectrophotometer was better than the ordinary colorimeter for the determination of dye concentration.

The dye method for the determination of plasma volume has been verified by radioactive iron methods.[3] More recently the dye method and the iodinated albumin method of measuring plasma volume have been found to correspond closely.[30]

Dieckmann and Wegner[5] in 1934 made the first study of the plasma and blood volume during pregnancy. Using Congo red as a dye substance they found at term an average increase in blood volume of 33 per cent in ten

obstetric patients examined. Thomson, Hirscheimer, Gibson, and Evans[34] using Evans blue dye found a 65 per cent increase in plasma volume by the ninth month of pregnancy. Bucht[1] found an increase in plasma volume of 25 per cent and stated that the plasma volume was slightly lower during the tenth month than during the eighth and ninth months of pregnancy. Tysoe and Lowenstein[35] in 1950 found that at the ninth month the blood volume was increased 34.8 per cent, plasma volume was up 44.3 per cent, and the red-cell volume was up 19 per cent.

Evans Blue Dye (T-1824)

Dawson, Evans and Whipple[4] in 1920 found that Evans blue dye by virtue of its blue color was easily read colorimetrically, and that hemolysis did not interfere with the reading. It is a diazo dye and has been shown to be practically nondiffusible when it is in protein combination. The rate of disappearance was found by Dawson, Evans, and Whipple, and others[10, 28] to be approximately 5 to 8 per cent per hour.

Rawson[29] and others[28] have shown that Evans blue dye is bound selectively in a complex to the plasma proteins. It is the strength of this bond that determines the rate of disappearance of the dye. The dye is eliminated from the blood stream by phagocytosis by the reticuloendothelial system, and to a much less marked degree by diffusion and excretion by the liver. It will not appear in the urine if the kidneys are normal and will not appear in edema or ascitic fluid. It will not pass the placenta or appear in the amniotic fluid.

Hueper and Ichniowski[19] concluded that the dye was not toxic in doses ordinarily used for hemodynamic determinations; however, repeated doses may produce slight nausea and vomiting. Ordinary doses will not discolor the skin or mucous membranes.

Methods

In the present study we have applied what we consider to be a modification of the Hamilton principle. These modifications have simplified the method without sacrificing accuracy. We have combined with the technique of determining the cardiac output a method for the determination of plasma volume, blood volume, red-cell volume, circulation time, pulmonary blood volume, and total peripheral resistance.

Evans blue dye was used in the undiluted form, i.e., a 4 per cent solution.* The concentrated form is considered most desirable for cardiac output determinations because a smaller volume may be used. The smallest volume possible, injected at the fastest possible rate, will produce the best results. The 4 per cent solution is satisfactory and produces accurate results.

It is very important that the injection syringe be calibrated by weight to deliver an exact amount of dye. The barrel and plunger of a 2 c.c. syringe were etched so that when the etched marks were superimposed the syringe would contain approximately 0.5 c.c. of dye. The syringe was then filled to

*Evans blue dye (4 per cent) used in this study was furnished by the William R. Warner & Co., Inc., Division of Warner-Hudnut, Inc., New York, N. Y.

this point with water and weighed on an analytical balance after an empty, dry, 20 gauge needle had been placed on the syringe. The syringe was then emptied through this needle and reweighed. The difference in weight, the calibration factor, when multiplied by the number of milligrams of dye per cubic centimeter gives the exact number of milligrams of dye delivered by that particular syringe when filled to the etched marks.

A standard concentration curve was prepared for each lot of dye. Several successive dilutions of dye were made in plasma and the optical densities determined. These densities were then plotted on linear graph paper against the concentration in milligrams per cubic centimeter. These points were then connected by the best straight line. From this standard curve the concentration of the unknown samples may be determined after the optical densities are obtained.

The patient's blood pressure and heart rate were taken before and after the determination. An average of the two readings was used as the correct blood pressure and heart rate. The blood pressure was measured with a standard mercury manometer using the patient's left arm.

The dye injection was made into an antecubital vein with the arm elevated on a pillow so that the point of injection was approximately level with the right atrium.

Kinsman, Moore, and Hamilton[21] have observed that it makes no difference from which artery the samples are taken or what size needle is used for sampling. Our apparatus for the collection of the arterial samples is simple yet effective. The hub was removed from an ordinary 2 inch, short bevel, 18 gauge needle, leaving only the shaft. A piece of polyethylene tube approximately 6 to 8 inches long and of proper internal diameter to fit tightly over the needle shaft was used. The shaft of the needle was held with a hemostat during the arterial puncture and collection of the samples. It is not necessary to sterilize the polyethylene tube or the hemostat, and the polyethylene tube may be discarded after the procedure.

Twenty sample tubes are required and are held in an ordinary test tube rack. An assistant held the rack at an accessible point so that the polyethylene tube reached each tube in succession. Two drops of liquid heparin were used in each tube as an anticoagulant.

The femoral artery, being the most accessible, was used for the collection of the arterial samples. The area of skin over the femoral triangle down to and around the femoral artery was infiltrated with a Novocain-Wydase solution. A 20 gauge needle on an ordinary 10 c.c. syringe containing a few drops of heparin was introduced into the antecubital vein. The collection needle was then introduced into the femoral artery by palpation. While the control sample was being collected from the artery, the injector exchanged the empty syringe for the calibrated syringe containing the dye. After the control sample was collected the dye was injected instantaneously and the timer* started. Ten samples were then collected at 3 second intervals for 30

*Precision Time-it, calibrated in seconds and tenths of seconds. Manufactured by the Precision Scientific Company, Chicago, Ill.

seconds, two at 6 second intervals for 12 seconds, two at 12 seconds for 24 seconds, two at 30 seconds for 60 seconds, and three at 60 second intervals, all being collected consecutively. This gives a total of one control and nineteen unknown samples over a period of 6 minutes. The needle was then withdrawn and pressure held over the point of arterial puncture for 5 minutes. No complications developed as a result of the punctures.

Approximately 2 c.c. of blood were collected in each unknown sample and 4 c.c. in the control. The polyethylene tube and the needle held only 0.18 to 0.20 c.c. by actual measure and a small amount of blood was allowed to escape between samples so that no error was introduced by blood remaining in the collection tube from one sample to another.

The samples were centrifuged at 2,000 r.p.m. for 10 minutes in an International Centrifuge, Size 2. The plasma was then pipetted into the microcuvettes and the optical density of each sample was determined in a Coleman Junior Spectrophotometer at a wave length of 620 mμ. The hematocrit was obtained from the control sample and was centrifuged in a Wintrobe tube at 2,000 r.p.m. for 45 minutes. From the standard concentration curve the optical densities were converted into milligrams per cubic centimeter. Each concentration was then converted into a unit or factor,

$$\frac{\text{mg./c.c.}}{\text{mg. injected/gram of body weight}}.$$

The numerator of this factor is the concentration of the sample and the denominator is obtained by dividing the milligrams of dye injected by the body weight in grams. These factors were then plotted on semilogarithmic paper against time expressed in seconds (Fig. 1). The same mathematical relationship between the logarithms of these factors occurs as does the relationship between the logarithms of the concentrations alone because the factors are directly proportional to the concentrations. Therefore, our curve has the same form as the curves described by Kinsman, Moore, and Hamilton.[21] The descending slope of the primary curve forms a straight line and can be extrapolated to the base line. The primary circulation curve is the curve that would be obtained if there were no recirculation. The actual curve obtained shows a secondary rise followed by several undulations due to recirculation. Mixing was complete within three minutes in every determination.

The concentration curve, after mixing was complete, was then extrapolated back to zero (Fig. 1). This gives what the virtual concentration would have been if mixing were instantaneously complete without disappearance of the dye. The reading at the extrapolation point was then used to calculate the plasma volume according to the following:

$$\frac{\text{mg./c.c.}}{\text{mg. injected/gram}} = \frac{\text{mg.}}{\text{c.c.}} \times \frac{\text{gram}}{\text{mg.}} = \frac{\text{gram}}{\text{c.c.}}$$

$$\frac{1}{\text{gram/c.c.}} = \text{c.c./gram}$$

c.c./gram × 1,000 = c.c. (of plasma)/kilogram

c.c./kg. × kilograms of body weight = total plasma volume.

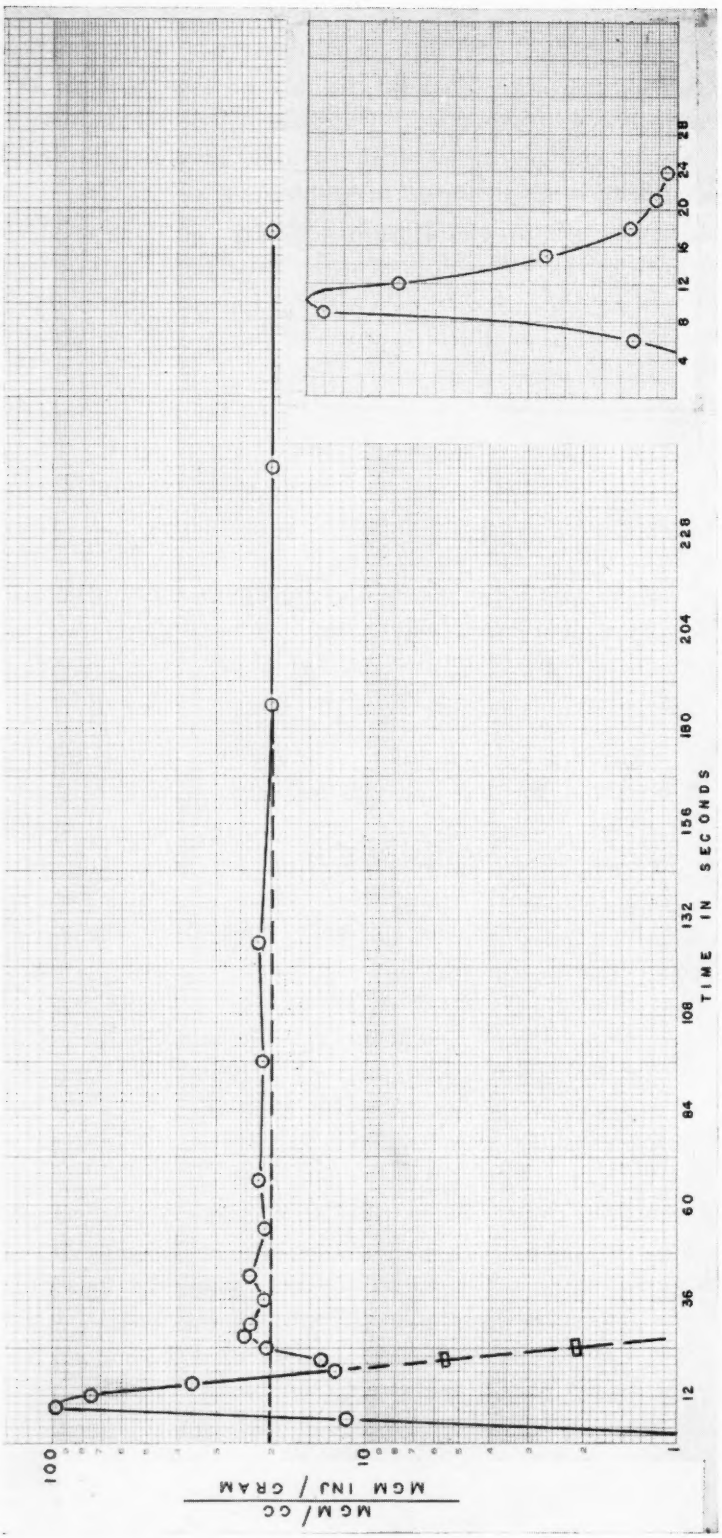

Fig. 1.—A typical time-concentration curve for the dye T-1824 in a pregnant woman. *Inset,* Arithmetic replot of the primary circulation curve.

Actually, by dividing the extrapolation reading into one, the result is in cubic centimeters of plasma per gram of body weight.

$$\text{Total blood volume} = \frac{\text{plasma volume}}{1 - \text{hematocrit}}$$

$$\text{Red-blood cell volume} = \text{blood vol.} - \text{plasma vol.}$$

As a means of checking the accuracy of these calculations several determinations were calculated, both by dye concentration alone and by this concentration-weight relationship. In no case was the difference greater than 1 per cent.

The cardiac output is calculated from the amount of dilution of the dye by the blood passing through the heart during the primary circulation. The primary circulation curve was replotted on linear millimeter paper in order to obtain a linear relationship between the concentration units or factors and time expressed in seconds (Fig. 1, insert). The area beneath this curve was measured with a Keuffel-Esser planimeter. The planimeter was calibrated by reading 1,000 unit-seconds and calculating the reading of 1 unit-second. The planimeter reading of the area beneath the curve was divided by the reading of 1 unit-second. Thus the number of unit-seconds beneath the curve is obtained. The number of unit-seconds beneath the curve was then divided into the weight of the patient in grams. The result is the cardiac output in cubic centimeters of plasma per second. Proof of this is shown by the following mathematical exercise:

$$\frac{\text{mg./c.c.}}{\text{mg. injected/gram}} \times \text{t (sec.)} = \text{unit-second}$$

$$\frac{\text{mg.}}{\text{c.c.}} \times \frac{\text{gram}}{\text{mg.}} \times \text{t} = \frac{\text{gram} \times \text{t}}{\text{c.c.}}$$

$$\frac{\text{grams}}{\text{gram} \times \text{t/c.c.}} = \frac{\text{grams}}{1} \times \frac{\text{c.c.}}{\text{gram} \times \text{t}} = \text{c.c./t or c.c. per sec.}$$

This is the output in cubic centimeters of plasma per second. It is converted into cubic centimeters of blood per second by use of the hematocrit and the formula given above for blood volume.

$$\text{Minute volume} = \text{c.c. per sec.} \times 60$$

$$\text{c.c. per minute per kilogram} = \frac{\text{minute-volume}}{\text{kilograms of body weight}}$$

$$\text{Stroke volume in c.c.} = \frac{\text{minute volume}}{\text{heart rate per minute}}$$

$$\text{Cardiac index (liters/minute/sq. meter)} = \frac{\text{minute volume}}{\text{sq. meters of body surface}} \div 1{,}000$$

The mean or average circulation time is the distance (in seconds) from zero to the peak of the primary circulation curve. It should be pointed out that this circulation time is the average circulation time from the point of injection to the point of sampling.

$$\text{Pulmonary blood volume (c.c.) (“Central” blood volume)} = \frac{\text{cardiac output (minute volume)} \times \text{circulation time}}{60}$$

$$\text{Mean blood pressure} = .44\ (\text{systolic-diastolic}) + \text{diastolic}$$

$$\text{Total peripheral resistance (Dynes per second per cm.}^5\text{)} = \frac{\text{mean B.P.} \times 1332}{\text{c.o. (c.c. per sec.)}}$$

Material

The patients used in this study were carefully selected from the outpatient prenatal clinic of the John Gaston Hospital. The determinations were begun at the time of the patient's first clinic visit and repeated at monthly intervals during the course of her pregnancy. In most cases determinations were also done immediately after delivery and at least once during the postpartum period. Repeated determinations on the same individual are much more significant than individual determinations at various stages of gestation. In our study an average of three determinations were done on each patient, with as many as six on several patients. A total of 94 determinations have been done on 31 normal pregnant patients.

All patients selected for the determination were normal in every respect. The hematocrit was over 30 per cent, the blood pressure was below 140/90, and there was no history of heart disease. There were no signs, symptoms, or physical findings of organic heart disease.

All patients were admitted to the hospital at least twelve hours before the determination. For six hours prior to the procedure they were not allowed food or water and were required to remain at strict bed rest. No sedation was given at any time. The procedures were done as quickly and quietly as possible so as not to arouse apprehension.

Eight normal nonpregnant women were selected from the gynecological wards to serve as controls. The same criteria for hematocrit, blood pressure, and physical findings were required and the same conditions were met in the controls as were in the series of pregnant women.

TABLE I. AVERAGE HEMODYNAMIC VALUES FOR EIGHT NORMAL NONPREGNANT WOMEN SELECTED AS CONTROLS

Cardiac output:		Plasma volume:	
Liters per minute	6.3	Cubic centimeters per kg.	37.3
Cubic centimeters per min. per kg.	92	Total plasma vol. (c.c.)	2,793
Cardiac index	3.6	Blood volume:	
Stroke volume (c.c.)	84	Cubic centimeters per kg.	64.2
Mean blood pressure (mm. Hg)	91	Total blood vol. (c.c.)	4,492
Circulation time (sec.) (arm to leg)	11.0	Red-cell volume:	
Central blood volume (c.c.)	1,331	Cubic centimeters per kg.	24.5
Per cent, $\frac{\text{central blood vol.}}{\text{total blood vol.}}$	31	Total red-cell vol. (c.c.)	1,699
Total peripheral resistance	1,178	Hematocrit vol. per cent	38.4

Results

The average results in the eight nonpregnant women selected as controls are shown in Table I. These results for nonpregnant women are quite similar to those of other investigators using the dye dilution technique.[1, 14]

Cardiac Output.—

The increase in cardiac output begins toward the end of the first trimester. There is a rather constant, rapid rise reaching a peak at approximately 28 weeks' gestation (Fig. 2). This rise is from the nonpregnant level of 6,327 c.c. per minute (6.3 L. per minute) to 8,346 c.c. per minute (8.3 L. per minute). This is an increase of 32 per cent at the point of maximum output. As pregnancy progresses beyond this point there is a definite decrease in output. The cardiac output shows a gradual decline reaching nonpregnant levels or lower at 38 to 40 weeks' gestation. At 40 weeks the output is 5,545 c.c. per minute (5.5 L. per minute). Immediately following delivery the output rises suddenly and dramatically to 7,139 c.c. per minute (7.1 L. per minute). This is an increase of 29 per cent over the output in the latter few weeks of pregnancy. The increased cardiac output is maintained over the first few days of the postpartum period; however, the nonpregnant level is reached by the end of the second postpartum week. Repeat determinations at six weeks post partum showed no significant difference from the two weeks post partum values.

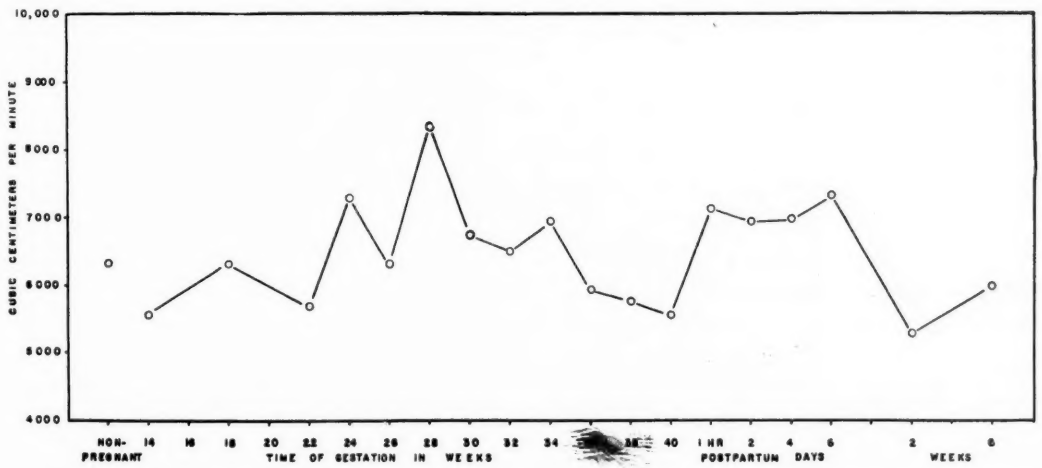

Fig. 2.—The average cardiac output in cubic centimeters per minute during normal pregnancy and the puerperium.

Alterations in the cardiac output during pregnancy are produced primarily by variation in stroke volume (Fig. 3), the heart rate remaining relatively constant throughout pregnancy and the puerperium. The average stroke volume in nonpregnant women was 84 c.c. At 28 weeks' gestation the stroke volume was 98 c.c. and at 40 weeks' gestation it had dropped to 67 c.c. Immediately following delivery the stroke volume was 92 c.c. The largest stroke volume occurs at the point of maximum cardiac output.

Plasma Volume.—

The increase in plasma begins at about the end of the first trimester. The rise in plasma volume is a gradual, prolonged process and does not reach a maximum until 32 to 34 weeks' gestation. This is 4 to 6 weeks later than the maximum output. When the plasma is expressed as total plasma volume there is no significant decrease during the last trimester to correspond to the decrease in cardiac output. Bucht[1] considered that Caton, Roby, Reid, and Gibson[2] statistically proved a reduction of the plasma volume during the last few weeks of pregnancy. A review of the data published by these investigators shows that, although their data perhaps suggest that such a decrease exists, conclusive proof is lacking.

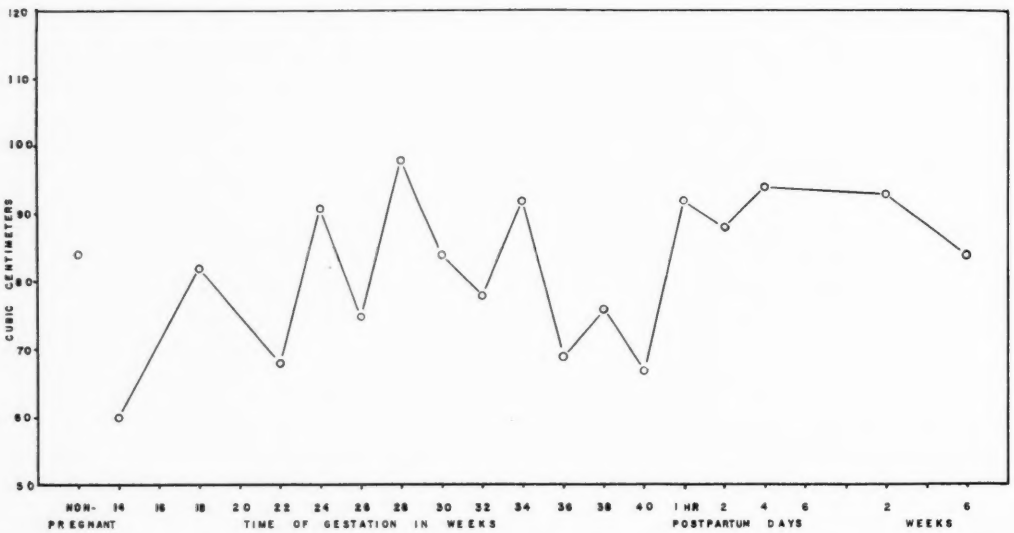

Fig. 3.—The average stroke volume in cubic centimeters during normal pregnancy and the puerperium.

The plasma volume increases from an average level in the nonpregnant of 2,793 c.c. to 3,396 c.c. at 34 weeks (Fig. 4). This is an increase of 22 per cent. During the last month to 6 weeks the plasma volume remains more or less constant. At the time of delivery the plasma volume drops due to blood loss. During the first 2 weeks of the postpartum period there is a readjustment to nonpregnant levels.

Blood Volume.—

The blood volume tends to parallel the plasma volume depending upon the individual hematocrit. The blood volume increase during pregnancy is relatively less than the plasma volume increase. This results in hemodilution with a consequent fall in hematocrit. The point of maximum hemodilution corresponds with the point of maximum plasma volume.

The blood volume increases from a nonpregnant level of 4,492 c.c. to 4,975 c.c. at 34 weeks of gestation, producing an increase of 11 per cent. The blood volume remains relatively constant during the last 6 weeks of pregnancy.

Hematocrit.—

We have purposely omitted from this study any patient having a hematocrit of less than 30 per cent. Consequently, the average hematocrits given here are not completely representative of the obstetrical patients of this area.

The values do bear out the old dictum that the hematocrit decreases as pregnancy progresses. In the average nonpregnant patient the hematocrit was 38.4 per cent. The lowest hematocrit was 31.1 per cent and this occurred at 32 weeks' gestation, the approximate point of greatest plasma volume (Table II). The decrease in the hematocrit is due to the relatively greater increase in plasma volume over the red-cell volume and is sometimes called a

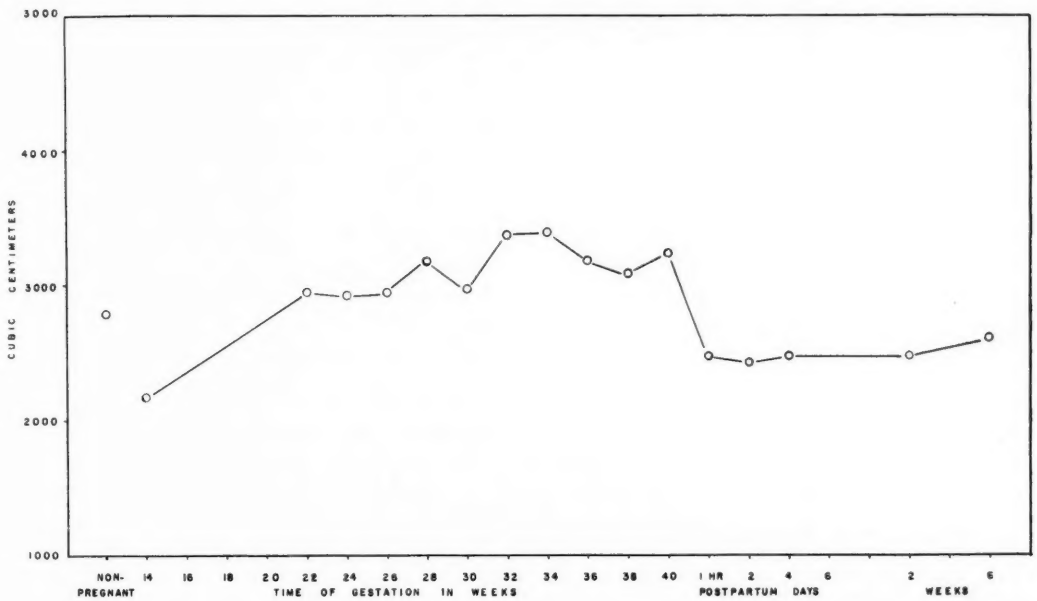

Fig. 4.—The average total plasma volume during normal pregnancy and the puerperium.

physiological anemia. During the last 6 weeks of pregnancy the hematocrit gradually rises. Due to blood loss with resultant hemoconcentration, the hematocrit rises during the first day post partum. During the next few days the hematocrit again falls due to the imbibing of extravascular fluid. It is gradually increased back to normal during the following weeks as the body replaces the red-cell volume.

TABLE II. AVERAGE HEMATOCRIT VALUES DURING NORMAL PREGNANCY AND THE PUERPERIUM

		Ante Partum									
WEEKS' GESTATION	NONPREGNANT	14	22	26	28	30	32	34	36	38	40
Hematocrit	38.4	39.6	31.8	31.8	33.3	32.4	31.1	31.7	32.5	33.4	31.7

Post Partum					
IMMEDIATELY	2 DAYS	4 DAYS	6 DAYS	2 WEEKS	6 WEEKS
37.2	39.0	34.1	34.3	37.2	40.2

Circulation Time.—

The circulation time is subject to much individual variation. The circulation time as calculated in this study is the time required for the dye to travel from the antecubital vein to the femoral artery. This may be termed the average pulmonary or "central" circulation time. The circulation time for normal nonpregnant women was 13.3 seconds. The circulation time during the early months of pregnancy tends to be normal or less than normal. At the point of maximum plasma volume the circulation time is at its lowest point (11.3 seconds). From this point to term the circulation time gradually rises reaching 15.8 seconds at 40 weeks. Immediately post partum the circulation time is decreased to 12.7 seconds. During the first 2 weeks of the postpartum period the circulation time adjusts to normal prepregnant control values.

"Central" Blood Volume.—

The pulmonary or central blood volume when measured with the dye technique is actually the volume of blood between the point of injection and the point of sampling. This also includes the blood in the other large arteries as well as the femoral. It includes all the blood that flows to and from the heart during the arm-to-leg circulation time.

The central blood volume is greater during pregnancy than in the nonpregnant state. This is true partially because of the dilated uterine vessels as well as the increased cardiac output. The central blood volume tends to parallel the total blood volume. In the nonpregnant state the central blood volume was 1,331 c.c. or 31 per cent of the total blood volume. During pregnancy the range was 1,445 to 2,306 c.c. The percentage of the total blood volume ranges from 30 to 39 during pregnancy.

Mean Blood Pressure.—

It is generally considered that the mean blood pressure during pregnancy is decreased. Our findings tend to support this belief. The mean blood pressure reaches its lowest level at approximately 36 weeks of gestation (Table III). It is, for the most part, the arteriovenous shunt effect of the placenta that brings about this decrease in blood pressure.

TABLE III. AVERAGE MEAN BLOOD PRESSURE DURING NORMAL PREGNANCY AND THE PUERPERIUM

	Ante Partum										
WEEKS' GESTATION	NONPREGNANT	14	24	26	28	30	32	34	36	38	40
Mean Blood Pressure	91	87	88	77	81	78	79	84	74	87	80

Post Partum				
IMMEDIATELY	2 DAYS	4 DAYS	6 DAYS	2 WEEKS
90	79	84	96	100

Total Peripheral Resistance.—

For the most part the energy of the blood at the periphery is dissipated as friction. The peripheral resistance represents the force against which this

energy must work. According to Wiggers and Middleton[41] the total peripheral resistance depends upon the physical dimensions of the vascular system, the viscosity of the blood, and the caliber of the arterioles. As long as the arterial pressure remains constant the total peripheral resistance indicates the quantity and direction of vasomotor activity.

The reduction in total peripheral resistance during pregnancy is thought to be largely the result of the decreased blood pressure. The blood pressure is reduced by the influence of the enlarged maternal sinuses and the arteriovenous shunt effect of the placenta. The increased cardiac output, the decrease in blood viscosity due to hemodilution, and the increased vascularity of the pelvic organs also tend to reduce the peripheral resistance.

The average nonpregnant TPR was 1,178 dynes/sec./cm.[5] As pregnancy progresses the TPR falls, reaching the lowest level at 28 weeks of gestation, the time that the cardiac output is greatest (Table IV). Following this, the TPR gradually rises until the time of delivery. Immediately following delivery the TPR falls slightly due to the increased cardiac output that occurs at this time. During the first two weeks of the puerperium the TPR gradually adjusts itself to nonpregnant levels.

TABLE IV. AVERAGE TOTAL PERIPHERAL RESISTANCE DURING NORMAL PREGNANCY AND THE PUERPERIUM

		Ante Partum									
WEEKS' GESTATION	NONPREGNANT	14	22	24	26	28	30	32	34	36	40
TPR	1,178	1,302	1,021	1,005	1,038	897	966	987	965	1,154	1,123
		Post Partum									
IMMEDIATELY		2 DAYS		4 DAYS			6 DAYS			6 WEEKS	
1,029		923		1,011			965			1,192	

Comment

The initial rise in cardiac output that occurs early in the second trimester is probably the result of reflex stimulation from the increased requirements of the growing products of conception. In response to the demands for an increased oxygen and food supply to the rapidly growing fetus, the maternal organism must increase the blood flow to the uterus and placenta. The cardiac output being controlled by reflexes will increase *pari passu* with the need for greater blood flow.

The increase in plasma volume, on the other hand, is a slow process requiring several weeks. The plasma increase requires the gradual imbibing of fluid from the extravascular space and the building up of the plasma protein and formed elements. Thus the cardiac output can increase much more rapidly than the plasma volume. For this reason the cardiac output reaches a peak from 4 to 6 weeks earlier than the plasma volume.

As the plasma volume increases the high cardiac output is no longer needed. The increased blood volume fills the maternal sinuses and supplies the fetus. The cardiac output gradually declines as the blood and plasma volumes reach a maximum. The output has reached its original nonpregnant level at 38 to 40 weeks' gestation.

Following delivery there are two factors which account for the sudden increase in cardiac output. The uterus has been emptied and as it contracts the extra blood volume is squeezed from the maternal sinuses into the systemic circulation. Also, the pressure of the uterus on the great veins of the abdomen has been released. Both these factors mean an increase in venous return to the heart and therefore an increase in cardiac output.

In grouping the data of this study according to the age of the patient and multiparity it was noticed that there is a definite tendency for greater degrees of change in the older individuals and in those having had the greatest number of previous pregnancies. This was not proved statistically, although there is a definite suggestion that this is true.

In dealing with pregnant patients there is a rather unique problem as to weight and surface area relationships. The same rules that hold for the nonpregnant state cannot be applied to pregnant individuals. This is particularly true in relation to hemodynamics as measured by the dye technique. Dieckmann and Wegner recognized that it was unreliable to express the plasma volume as function of weight under these conditions.

The Evans blue dye will not pass the placenta and therefore will not circulate through the fetus, cord, amnion, or amniotic fluid. The dye also does not penetrate the extravascular space. This tissue, as far as the dye circulation is concerned, is "avascular" tissue. This is to be contrasted with the "vascular" tissue increases during pregnancy such as hypertrophy of the uterus, adnexa, breasts, and endocrine glands.

During the second trimester there is a rapid gain in the weight of the pregnant individual. This weight gain is largely "vascular" tissue gain through which the dye circulates. Therefore, there is no discrepancy when the hemodynamic functions are expressed in terms of body weight during the first two trimesters.

During the third trimester the products of conception tend to gain weight rapidly. There is also a rapid increase in extracellular fluid at this time. The rapid "avascular" weight gain during the third trimester is not measured by the dye circulation. Therefore, a definite error is produced when the plasma volume or cardiac output is expressed in terms of kilograms of body weight. This means that the hemodynamic values, if expressed in this manner, tend to be erroneously low during the third trimester. Furthermore, the values will become progressively lower as the pregnancy nears termination.

If our data are expressed as plasma volume per kilogram, the plasma volume is 10 per cent lower at term than at 34 weeks. Investigators who have previously reported reductions in plasma volume during the last trimester were probably making this assumption on the basis of the plasma volume per kilogram. There is no significant drop in plasma during the last trimester when it is expressed as total plasma volume.

The cardiac output, on the other hand, definitely decreases during the last trimester and expressing it in terms of cubic centimeters per minute per kilogram only serves to accentuate the reduction.

From a clinical viewpoint, an analysis of these data shows that there are two periods during pregnancy and the puerperium in which the cardiovascular system is placed under a strain. The cardiac output must increase to almost unbelievable levels at approximately 28 weeks' gestation and immediately post partum.

A normal heart has no difficulty compensating for the increased work load. However, it may be impossible for a diseased heart so to compensate. A patient may experience cardiac decompensation for the first time during these two critical periods. Heart failure during the first trimester may be expected to be intensified during the critical period.

If a patient with cardiac disease becomes pregnant she may be expected to experience difficulty at the end of the second trimester or immediately post partum. If she can be carried past the twenty-eighth week, in all probability her condition will improve during the last trimester. It is also true that if a pregnant patient with cardiac decompensation passes the twenty-eighth week safely she may be expected to pass the immediate postpartum period with little or no difficulty because the latter strain is no more than that already passed. Therefore, termination of pregnancy in patients during the last trimester because of cardiac decompensation is not physiologically sound.

Summary

1. A new method for the determination of cardiac output and plasma volume in man based upon the Hamilton dilution principle has been presented. The method is simple, accurate, requires very little equipment, and can be applied clinically. Repeated determinations can be made on the same patient with no discomfort to the patient. It is technically easier and produces less apprehension than any other method available for the determination of cardiac output. With the same procedure, requiring only six minutes, one can measure the plasma volume, blood volume, red-cell volume, cardiac output, mean pulmonary circulation time, pulmonary or "central" blood volume, and the total peripheral resistance.

2. We have made 94 determinations in 31 normal pregnant women. Serial determinations were made on each patient at intervals of four to five weeks during the pregnancy. Determinations were also made immediately following delivery and during the puerperium. On several patients as many as six determinations were made.

Eight normal nonpregnant women were selected as controls and determinations were made in the same manner as those in the pregnancy series. The patients were as near basal conditions as possible at the time of each determination.

3. The cardiac output during pregnancy rises rapidly from the end of the first trimester to a maximum at 28 weeks' gestation. This increase amounts to 32 per cent over the nonpregnant levels. Following this peak there is a definite decrease as the pregnancy progresses. The original nonpregnant level is reached at approximately 38 to 40 weeks. Immediately following delivery

there is another rapid increase in cardiac output amounting to 29 per cent. The nonpregnant levels are again reached by two weeks post partum.

The alterations in cardiac output are produced by stroke volume changes. The stroke volume tends to parallel the minute volume with the heart rate remaining relatively constant.

4. The plasma volume increases during normal pregnancy; however, the change is much slower than that found in the cardiac output. The maximum plasma volume is attained at approximately 32 to 34 weeks' gestation. This increase amounts to 22 per cent at this point. There is no significant decrease in plasma volume during the last trimester. The red-cell volume also increases during pregnancy but to a much less degree. This produces a hemodilution or physiological anemia that is greatest at the point of maximum plasma volume. Therefore, the hematocrit during normal pregnancy is lowest at 32 to 34 weeks' gestation.

5. The circulation time was found to decrease from an average of 13.3 seconds to 11.3 seconds at 34 weeks' gestation. From this point it gradually rose, reaching 15.8 seconds at 40 weeks.

6. The central blood volume was found to be greater during pregnancy than in the nonpregnant state. It tends to follow the blood volume and cardiac output changes, being greatest at the point of maximum cardiac output.

7. The changes in the mean blood pressure and total peripheral resistance are definitely related and tend to change in the same direction. During normal pregnancy the total peripheral resistance and mean blood pressure decrease, reaching the lowest levels at the point of maximum cardiac output. This decrease is thought to be due to the enlarged maternal sinuses, the arteriovenous shunt effect of the placenta, the increased cardiac output, and the decreased viscosity of the blood.

8. It was necessary to establish the normal levels in pregnancy before studying pathological conditions. The comparison between the normal and the abnormal may effect changes in therapeutic measures. It is thought that this new method may prove to have practical value.

I should like to express my deepest appreciation to those who made this work possible: My wife, Genevieve Adams, who aided immensely in the preparation of the manuscript; Miss Dorothy Fair, who not only gave excellent technical assistance but also helped in the analysis and arrangement of the data; Richard R. Overman, Ph.D., Professor of Clinical Physiology, University of Tennessee, who aided in the initiation and progress of the project with his kind, intelligent guidance; Frank E. Whitacre, M.D., formerly Chief of the Division of Obstetrics and Gynecology, University of Tennessee, who presented the opportunity and stimulated it with an unsurpassable inspiration.

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UTERINE CLOSURE IN CESAREAN SECTION*

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A SIMPLIFIED method of closing the uterus used in 114 cases of cesarean section was reported before this association in 1941.[1] At that time, a marked improvement in the results was seen over those with the previous terraced closure techniques. One maternal death was reported in that series, which was due to excessive beveling of the endometrium, a practice which has now been discontinued.

Today, after experience with over 5,000 cases of cesarean section, including 1,521 cases since 1941, using an improved simplified technique, we have had an excellent opportunity of comparing results of the new and old type of closure in approximately 500 repeat sections by examination of the old scar.

During this twelve-year series of 1,521 cases, no maternal deaths and no ruptures of the uterus have occurred.

Two cases of uteroperitoneal fistula comprised the most important untoward results in this series of 1,521 cases of cesarean section.

Generally in this series there was a lack of postoperative complications, no uterine ruptures, and at repeat sections histologically improved scars were seen with practically no adhesions.

The improved uterine closure technique has been used with excellent results in both high classical and low cervical sections.[2] It is not the purpose of this paper to argue the pros and cons of high versus low section, but to point out that improved uterine scars may be obtained by employing the technique to be described.

Irving Siegel,[3] in the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY for December, 1952, cites the incidence of rupture following high section as 4 per cent and that after low section as 0.25 per cent at subsequent pregnancy. In this series of 1,521 cases there have been no ruptures. Robert Hodkinson,[4] in the *British Medical Journal* for February 9, 1952, reviewing statistics, states that although there is a much lower over-all incidence of rupture in low-segment scars, when they do weaken and rupture, the maternal mortality far exceeds that of the classical scar rupture. Low-segment rupture is often extraperitoneal, with concealed hemorrhage, whereas in high-segment rupture, hemorrhage is more limited by uterine contractions; also by the fact that it is more likely to be recognized sooner by production of the symptoms of the acute abdominal crisis.

*Presented at the Sixty-fourth Annual Meeting of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons, Hot Spring, Va., Sept. 10, 11, and 12, 1953.

Since the prognosis of a subsequent pregnancy and possible labor in patients who have had previous cesarean sections depends on (1) the likelihood of occurrence of rupture of the uterus, and (2) the likelihood of maternal death in the event of rupture, high section has been the one of choice, although the method has been used in both types of section with excellent results and both types will be described.

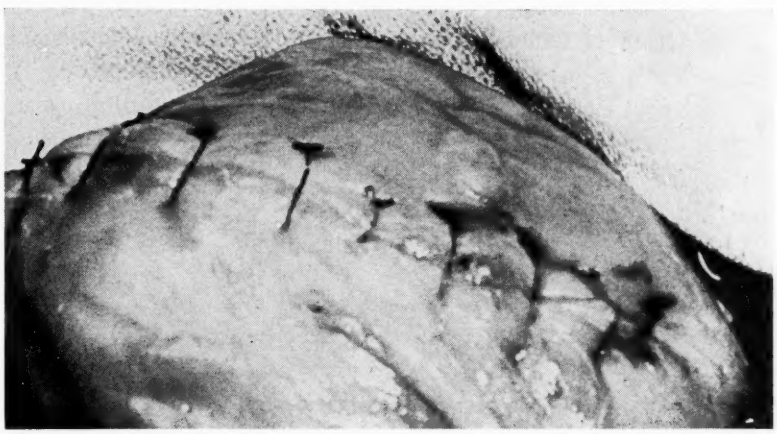

Fig. 1.—Uterine closure by interrupted silk sutures through the outer third of the myometrium.

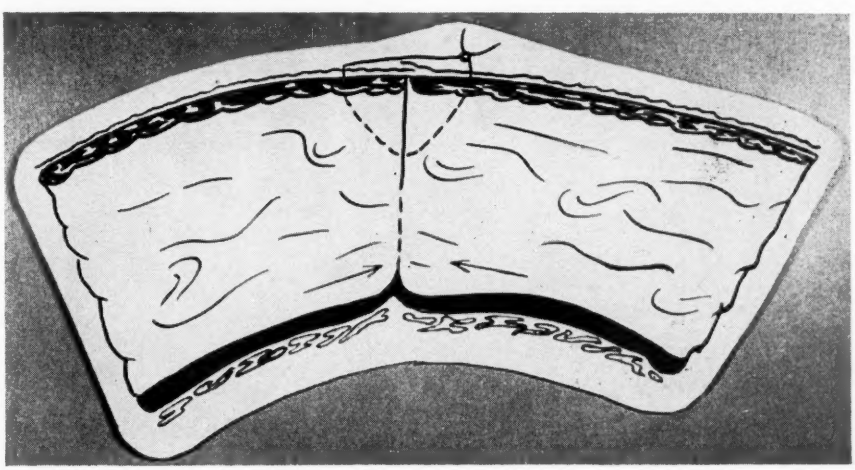

Fig. 2.—Closure technique, schematic, illustrating physiologic placement of suture, with knot to one side of the midline.

Method

In the high classical section, previous uterine scars are examined prior to incising the uterus. A new incision is made adjacent to the often inconspicuous old uterine closure line (identified only by the residual silk sutures) and the thickness of the scar is tested before the uterus is emptied.

Following evacuation of the uterus, the fundus is exteriorized and grasped firmly from the posterior aspect in the left hand of the operator. This aids in

hemostasis and correct approximation of the myometrium. At this time, the scar of a previous section is often resected for pathologic study. Undercutting of the endometrial surface has been discontinued except in instances in which the endometrial tissue is superfluous or pouting.

The incision is closed by interrupted silk sutures through the outer third of the myometrium, the operator using a long, straight, round-pointed needle in the right hand while holding the fundus firmly in the left hand. Suturing is begun 1 cm. from the incision, the silk sutures passing through the myometrium at a depth of approximately one-third the thickness of the uterine wall. The sutures are placed about 2 cm. apart and tied by an assistant. It is important that the knots be kept to one side of the incision, that they be cut close, and that they be tied only tightly enough to maintain coaptation of the myometrium but not so tightly that blanching ischemia of muscle tissue will result. Sliding of the suture along the incision during tying aids in obtaining exact alignment of the serosal surfaces.

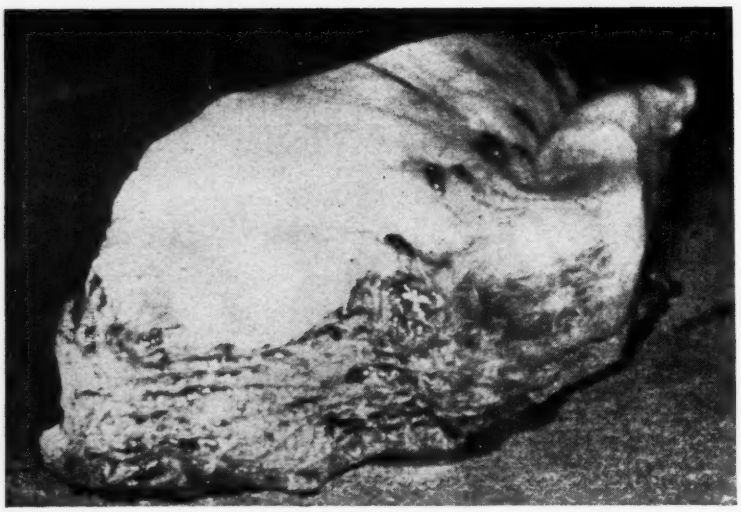

Fig. 3.—Gross view of resected uterine scar. The line of the scar is shown by the old silk sutures. The surface shown is cut through the scar and shows good uniformity across the old scar line.

Midway in the closure, the uterus is packed with iodoform gauze. It is thought that such packing stimulates uterine contractions, aids in drainage, acts as a mop to remove remnants of membrane, and, further, may promote regeneration of tissue. This pack is removed through the cervix after forty-eight hours. The closure is completed and the uterus replaced in the abdomen. Large blood clots are carefully removed, but the abdominal cavity is not mopped out. Pitocin is given at this time only after normal hemostasis has been effected. The abdomen is closed routinely with retention sutures and clips.

For low vertical and transverse cervical sections, the technique is varied only in that a bladder flap is freed, and, in closing, the interrupted silk sutures are placed, using a curved round needle, to a depth of one-half of the outer thickness of the myometrium. The bladder flap is closed over the silk sutures, using fine plain catgut. Three hourly doses of Ergotrate are given to ensure uterine contraction and physiologically control hemorrhage. Antibiotics are not used routinely.

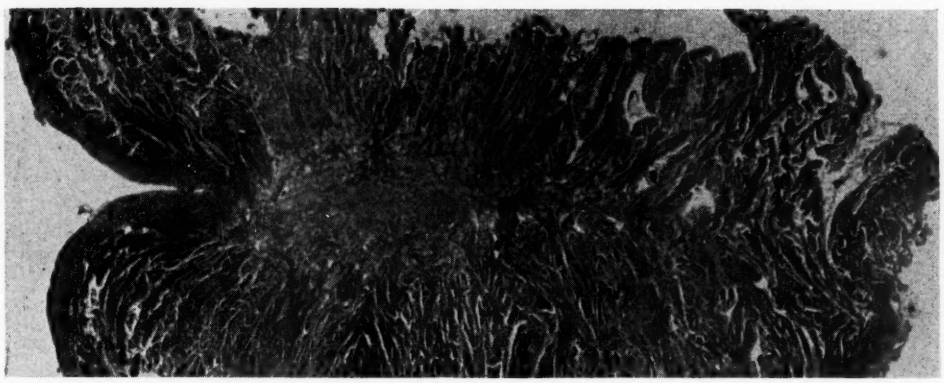

Fig. 4.—Uterine scar on histologic examination shows best muscle regeneration in the inner two-thirds of the myometrium, which healed by physiologic coaptation. (Hematoxylin and eosin stain. ×5; reduced ¼.)

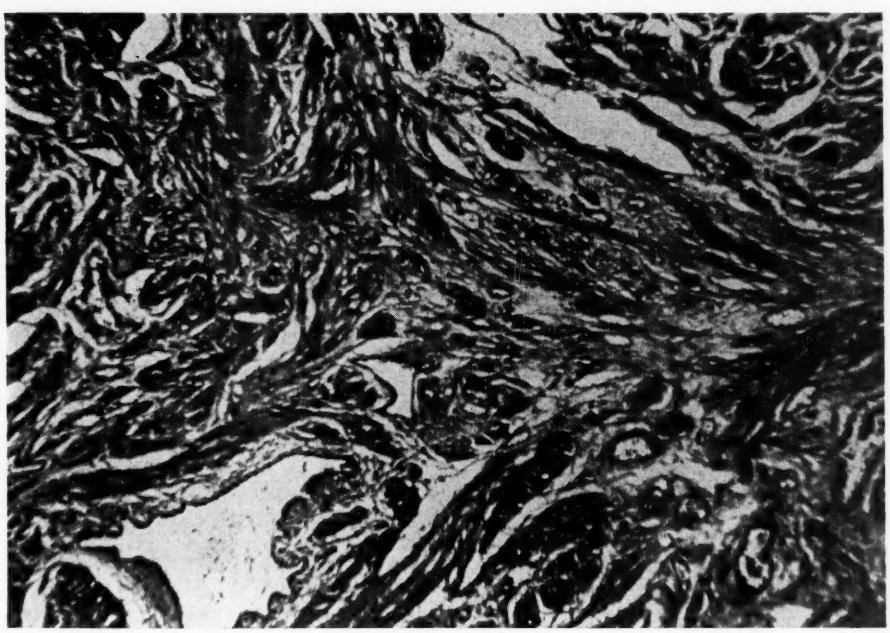

Fig. 5.—Muscle bundles may be seen crossing scar tissue in this scar in the midmyometrium. (Hematoxylin and eosin stain. Original ×12, this print ×60; reduced ¼.)

Fig. 6.

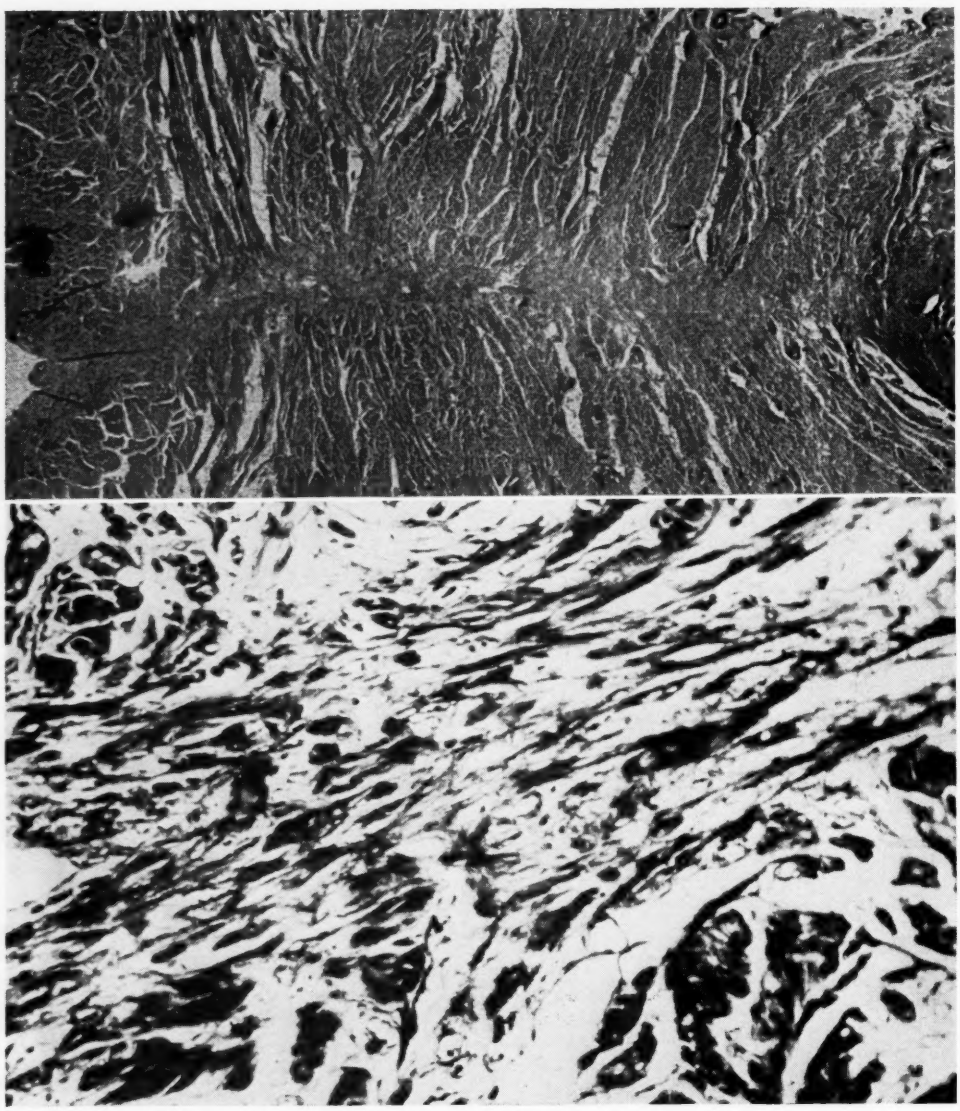

Fig. 7.

Fig. 6.—Uterine scar showing some connective tissue and many muscle bundles crossing the scar. (Hematoxylin and eosin stain. ×10; reduced ¼.)

Fig. 7.—High-power magnification of same scar shows predominance of muscle fibers through the mid-scar. (Masson stain. Original ×33, this print ×165; reduced ¼.)

Comment

In this mortality- and rupture-free series of 1,521 cesarean sections, it has also been proved to our satisfaction that this technique of uterine closure leads to minimal postoperative complications, such as nausea, emesis, ileus, and adhesions.

The single row of interrupted sutures placed in the outer third of the uterine wall leads to physiologic coaptation of the myometrium without the

hindrance of (1) foreign-body reaction to too much catgut, (2) strangulation of tissues by continuous sutures, leading to slough and infection, (3) lack of drainage of the myometrium, as in terraced suturing, which can cause further foreign-body reaction and eventually heavy scar tissue.

The technique (1) is rapid and time saving, (2) causes little or no ischemic necrosis due to suturing, (3) causes little or no suture reaction, (4) provides almost free drainage into the uterine cavity, collections of blood and infection which are potential producers of scar tissue being drained away, (5) keeps the peritoneal surface tightly closed, and (6) produces the uterine closure having the minimal amount of scar tissue.

We agree with the current concept that healing of an incision in the pregnant uterus takes place with the formation of connective tissue. We do wish, however, to point out that by proper coaptation of the myometrial edges without undue foreign-body reaction, ischemia necrosis, or myometrial infection, healing takes place with a minimum of connective tissue. Further, we have seen, in almost all cases in which the improved closure technique was used, a bridging of the connective tissue with regenerated smooth-muscle fibers, which in most instances predominated over connective tissue across the old closure. The usual pathological report describes smooth-muscle bundles crossing the scar which contains minimal connective-tissue elements. Indeed, examination of many scars shows the best union of the myometrial edges in the inner two-thirds of the wall which fell into automatic apposition, guided by the sutures in the outer third. Most of them show little or no noticeable retraction of serosal or endometrial surfaces. On cross section of the resected scar, the myometrial tissue usually appears to be almost continuous across the closure line. Exceedingly few adhesions have been found over the uterine closure area.

Summary

It is obvious, as shown in this series, that by the use of this technique of uterine closure, in which interrupted sutures are placed in only the outer third of the myometrium, better uterine scars with less retraction, less connective tissue, and more smooth-muscle regeneration will result, with fewer ruptures. The principle is that the minimum amount of nonreactive sutures required to hold in coaptation the myometrial edges, without producing ischemia, and still control hemorrhage, the better. Once the fear of uncontrolled hemorrhage of the uterine incision has been overcome, and surgeons realize the histologically and clinically improved results that can be obtained by such a technique, there will be less concern as to uterine rupture secondary to previous cesarean section, whether high or low.

We believe the value of the method has been proved by the paucity of postoperative hemorrhage and other sequelae, along with consistently improved uterine scars and the absence of a fatality or a rupture in this series of 1,521 cesarean sections over a twelve-year period in which the closure technique described here was used.

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Discussion

DR. J. P. GREENHILL, Chicago, Ill.—Does it matter how the uterine incision is closed at the time of cesarean section? If so, is there a difference in closure between classic cesarean sections and low cervical operations? The criterion of proper closure is usually a well-healed scar and such a scar should not rupture during pregnancy or labor. There are proportionately more ruptures after the classical operation than after the cervical one. Eames (Am. J. Obst. & Gynec. 65: 948, 1953) found that among 902 collected cases of classical scars, the incidence of rupture was 2.6 per cent and among 880 collected cases of low cervical scars, the incidence was 1.3 per cent—exactly half. However, Lane and Reid (Obst. & Gynec. 2: 54, 1953) found dehiscence or rupture of the cesarean section incision in 3 per cent of women who subsequently became pregnant. Furthermore, they believe that the classical incision is more likely to withstand the forces of labor than a lower segment scar. Which is the more important factor in wound healing and in rupture of the wound, the type of closure or the thickness and character of the muscle sutured?

All ruptures of the uterus do not occur in the scar. Many ruptures take place alongside the scar. What significance should be attached to this? Is there a difference in the frequency of rupture of the uterus when a transverse incision is made in the lower uterine segment as compared with a longitudinal incision? Lane and Reid say that in their series of repeat cesarean sections there was no difference in the susceptibility of rupture of the transverse, as contrasted with the longitudinal incision in the lower uterine segment. Are some of the ruptures of the longitudinal incision in the lower uterine segment due to improper closure, or to the fact that in many cases of cervical cesarean section the upper part of the incision is made in the corpus? After classical sections a rupture is usually a serious matter because the baby is nearly always lost and the uterus must usually be removed but in most cases of rupture following a cervical operation, the operator at the time of a repeat cesarean is surprised to find an opening in the lower uterine segment under the bladder peritoneum with the membranes bulging through. Furthermore, healing of a wound depends upon other factors as well as type of closure, for example, infection. Today infection is uncommon after cesarean section, even without the use of antibiotics.

I raise these questions because I believe it is difficult to appraise the full importance of the type of wound closure at cesarean section, whether it be the high or the low operation.

I firmly believe that too much catgut is used in the closure of most uterine incisions. Three or more layers are entirely too many, certainly in the lower uterine segment. Whether nonabsorbable suture material such as silk is better than catgut, I do not know. However, I am convinced that interrupted sutures yield better anatomical results than do continuous sutures regardless of the material used. Continuous sutures usually shut off too much blood supply and thereby may interfere with proper wound healing. I know of two instances where almost an entire continuous catgut suture was expelled per vaginam.

Many years ago with Benson Bloom (J. A. M. A. 92: 21, 1929) I made a study of 37 scars removed from uteri at the time of repeat cesarean section. From this study and from subsequent studies of scars, I have proved to myself at least that interrupted sutures (in all of my cases it was catgut) yielded better-healed uterine tissue than continuous sutures. At the present time I compromise between interrupted and continuous sutures. I never use more than two rows of sutures for closure and each row consists of two or three short pieces of continuous catgut. Since practically all of my operations are low cervical transperitoneal, and since there is seldom need to strangle the tissue to control bleeding, as in most classical operations, the sutures are not pulled tightly. However, in spite of several different types of closure, in my own series of 381 cervical cesarean sections I have encountered an occasional

hole in the lower uterine segment and several paper-thin muscle areas at the time of repeat operation. The former, of course, are ruptures of the uterus. I am afraid that I have not added anything to clear up the question of the proper closure of uterine incisions at cesarean section, but I have only raised several questions which are difficult to answer.

DR. POTTER (Closing).—The lack of discussion is surprising to me. I am convinced, however, that the method of closure is very important, and I feel, as does Dr. Greenhill, that the interrupted suture is the suture of choice. However, I feel that too many sutures are used and tied too tightly. I think that if we get away from the fear of hemorrhage, better results will be obtained.

THE MANAGEMENT OF BREECH PRESENTATION*

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(From the Department of Obstetrics, Medical College of Virginia Hospitals)

BREECH presentation is a serious complication in labor because of the high fetal mortality associated with it. A review of the literature reveals a wide difference of opinion as to the etiology of the presentation and the most effective methods of reducing fetal loss associated with breech presentation.

It is particularly difficult to compare statistics as reported in studies of patients with breech presentations because it is rare to find two authors who use the same standards for either the minimum weight of the babies reported or the maternal and fetal complications used in making corrections for infant mortality.

Clinical Material

In a study of any complication of pregnancy, we believe that all maternal and infant mortality occurring in patients with the complication should be reported as gross mortality, and the methods of correcting the mortality should be plainly stated. As several authors have used 28 weeks or more since the last known menstrual period as the minimum duration of pregnancy for the patients studied, we are reporting all of our patients pregnant 28 weeks or more. Following this plan, we found that with two exceptions the babies weighed 1,814 grams (4 pounds) or more. These two babies are included in this report.

The effect of minimum weight requirements is shown by the fact that during the last six years we could have reported 50 per cent less infant mortality in breech deliveries if we had excluded babies weighing less than 5 pounds, 8 ounces (2,494 grams). This illustrates the difficulty one encounters in comparing reports when the duration of pregnancy and minimum weight of the newborn are not stated.

We have reviewed the charts of all private patients with primary breech presentations at the time of delivery. There were 470 mothers in this group and 473 babies because, in three sets of twins, both babies presented as breech presentations.

The 473 breech deliveries occurred in 11,745 private patients delivered since September, 1928, an incidence of 4.02 per cent for breech presentations.

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All of the patients were attended by Drs. W. C. Winn, Eric C. Schelin, or the senior author. In this series of cases, we have included all patients with primary breech presentations, even those in whom the fetus was dead when the patient was first seen by us and patients first seen in consultation at the time of delivery. In six cases the fetus had died in utero before the onset of labor. Three mothers had eclampsia, and they were referred to us because of hypertension and convulsions.

General Impressions

The following are our impressions of the types of breech deliveries:

Spontaneous breech deliveries require no manipulation on the part of the physician and they are infrequent.

Breech extraction as carried out by us is a type of delivery implying some aid by the physician after the hips have delivered spontaneously.

Conversion and extraction includes those cases in which the entire baby was extracted, often by bringing down one or both feet.

We believe that each obstetrical patient must be treated individually. In patients with breech presentations, correct evaluation of several factors will reduce fetal and infant mortality. We try to determine accurately the size of the baby, particularly the size and attitude of the head, and the position of the arms. Extended arms during labor increase the difficulties at the time of delivery. X-ray examination late in pregnancy or early in labor will give valuable information as to the size of the baby, type of breech presentation, and the size and shape of the mother's pelvis. We try to determine the advisability of vaginal or abdominal delivery late in pregnancy, and before the onset of labor whenever it is possible.

Breech presentation occurs more frequently in premature births, twin pregnancies, polyhydramnios, and in cases where the baby fails to adopt an attitude of flexion. Multiparity and elderly primiparity seem also to be associated frequently with breech presentations.

Irving and Goethals,[11] Cannell and Dodek,[2] Siegel and McNally,[19] Seeley and Siddall,[18] Ryder,[17] Grimes and Bartholomew[8] report good results with external version late in pregnancy. The latter group report that they lowered the incidence of breech delivery in the period of viability to 2.6 per cent and for term breech delivery to 1.9 per cent in 7,433 consecutive cases taken from private practice.

We do not attempt routine external versions in our patients with breech presentations, but we do attempt to convert some breech presentations when the breech is not fixed in the pelvis and the membranes are intact. We have had limited success with this procedure. Breech presentations frequently convert spontaneously late in pregnancy. There are some real dangers associated with external version, particularly if much force is exerted. Our experience with external cephalic version has been disappointing.

Irving and Goethals[11] have advocated shortening the second stage of labor in breech delivery and emphasized the importance of deep anesthesia of the mother at the time of delivery.

From the literature it is evident that the majority of the physicians discussing breech presentations prefer deep anesthesia when extraction of the baby is indicated. Among the advocates are Irving and Goethals,[11] Potter,[16] Bill,[1] Dieckmann,[4] Mohler,[14] and Grimes and Bartholomew.[8] We[22] also believe in deep anesthesia when extraction of the baby is indicated.

The importance of full dilatation of the cervix before attempting a breech delivery has been emphasized by Bill,[1] Potter,[16] Grimes and Bartholomew,[8] Mohler,[14] Martindale,[12] and Irving and Goethals.[11] In the patients we have seen in consultation late in labor, a failure to recognize the importance of full dilatation and paralysis or loss of irritability of the cervix has been frequently observed. The incidence of fetal and infant deaths and birth injuries is increased enormously if the cervix is not completely dilated, retracted, and paralyzed when a vaginal breech delivery is attempted. This danger is ever present, particularly in footling presentations and premature births, because in these cases the feet frequently present at the vulva before the cervix is dilated enough for the head to be delivered without trauma.

Dieckmann[4] has advised individual evaluation for each patient with a breech presentation and I am sure we can all agree on this procedure. He states, "We do not believe in a routine prophylactic 'breaking up' of the breech and pulling down one or two legs, but we do use this procedure in selected patients where labor is unduly slow." We, too, have followed this plan. We have done total extractions in 15 per cent of our cases.

Episiotomy was performed 325 times in 383 vaginal deliveries, an incidence of 84 per cent for all vaginal deliveries. No third-degree laceration occurred in any of our vaginal breech deliveries. We think the frequent use of episiotomy has prevented maternal trauma and morbidity, fetal and infant mortality, and injuries to the infants. The two infant deaths recorded later as due to intracranial hemorrhage occurred in babies easily delivered vaginally. No other serious fetal injuries occurred except that five babies had fractured clavicles.

Statistical Analysis of Series

The more detailed analyses of special points in this series are shown in the accompanying tables.

Table I shows the number of mothers and babies in this report.

TABLE I. RELATION OF BREECH PRESENTATION TO SINGLE AND TO TWIN PREGNANCY

Total number patients (mothers)		470
Total number patients (babies)		473
Total number twin pregnancies (both breech)		3
Total number twin pregnancies (one breech)		31
Twin pregnancies, first baby breech	11	
Twin pregnancies, second baby breech	20	

Table II shows the percentage of primiparas and multiparas in the series and the approximate duration of the pregnancies. Eighty-four per cent were 38 weeks or more pregnant.

TABLE II. DURATION OF PREGNANCY

	28-32 WEEKS	32-38 WEEKS	38 OR MORE WEEKS	TOTAL
Primiparas	3	28	240	271
Multiparas	4	38	157	199
Total	7	66	397	470
Percentage	1.48	14.0	84.46	

Table III shows that 68 per cent of the presentations were frank breech and only 12 per cent were footling presentations.

TABLE III. TYPES OF BREECH PRESENTATIONS

	PRIMIPARAS	MULTIPARAS	TOTAL	PER CENT
Frank breech	198	128	326	68.92
Complete breech	42	46	88	18.60
Footling breech	32	27	59	12.47
Total	272	201	473	100

Spontaneous premature rupture of the membranes as shown in Table IV occurred in 32 per cent of all the patients in this series. Many of these patients were given a medical induction after the membranes had ruptured spontaneously. Amniotomy and medical inductions were used in patients with certain complications, chiefly those with toxemias. It is interesting to note that approximately 68 per cent of the patients went into labor spontaneously.

TABLE IV. ONSET OF LABOR

	NO. PATIENTS	PER CENT
Spontaneous	318	67.65
Medical induction	34	7.23
Medical induction and amniotomy*	47	10.
Premature rupture of membranes (spontaneous)	151	32.12

*Prolapse of the umbilical cord did not occur in any case in which the membranes were ruptured artificially.

Table V shows that the duration of labor was shorter in both primiparas and multiparas than the average given in most textbooks.

TABLE V. AVERAGE DURATION OF LABOR (VAGINAL DELIVERIES)

	FIRST STAGE		SECOND STAGE	
	HOURS	MINUTES	HOURS	MINUTES
Primiparas	9	39	1	18
Multiparas	8	12		36

The type of delivery is shown in Table VI. In this table breech extraction includes all cases in which any assistance was given in delivering the body, shoulders, and head except those included under conversion and extraction.

Breech converted and extracted as used in Table VI includes all complete extractions.

TABLE VI. TYPE OF DELIVERY

	PRIMIPARAS	MULTIPARAS	TOTAL	PER CENT
Spontaneous	32	33	65	13.74
Breech extraction	125	124	249	52.65
Breech converted and extracted	52	19	71	15.01
Forceps to aftercoming head	98	33	131	27.70
Cesarean section	59	29	88	18.60

In Table VII we have recorded the important maternal complications, some of which increased the fetal and infant loss. Although prolapse of the umbilical cord occurred twelve times, none of these babies were lost. This, we think, was due to the fact that one of us usually watched the breech cases very closely, and the fetal heart rate was recorded frequently after the onset of labor or rupture of the membranes.

TABLE VII. MATERNAL COMPLICATIONS

	PATIENTS
Prolapse of cord	12
Premature separation of placenta	6
Placenta previa	1
Polyhydramnios	5
Postpartum hemorrhage	16
Laceration of cervix	1
Toxemia (pre-eclampsia)	36
Toxemia (eclampsia)*	3

*All 3 patients with eclampsia were referred to us because of the eclampsia and several of the others were referred because of the complications listed above.

Table VIII shows the number of mothers delivered by cesarean section. The patients delivered by section were older than the average in the series and their babies were larger than the average for the entire series.

TABLE VIII. VAGINAL AND ABDOMINAL DELIVERY

Delivered vaginally	382 mothers	385 babies
Delivered by cesarean section*	88 mothers	88 babies

*The average age of the patients delivered by cesarean section was 29.5 years.
One baby delivered by cesarean section because of irregular fetal heart sounds, spontaneous premature rupture of the membranes, and cervix 3 cm. dilated, did not survive. All other babies delivered by cesarean section left the hospital in good condition.

Seeley,[18] Dennen,[3] and others have emphasized the importance of delivery of breech presentations by cesarean section when the mother's pelvis is contracted or the baby is excessively large. In an elderly primipara, even a moderate contraction of the pelvis may necessitate delivery by cesarean section. Other indications for delivery by cesarean section may be extension of the baby, particularly the head and arms, a rigid thick cervix, weak, ineffectual uterine contractions, and emotional disturbances in the mother.

The patient in labor with a breech presentation needs analgesia just as any other woman in labor. We vary the analgesia according to the patient's needs and the probable duration of her labor. In recent years we have used smaller doses of analgesia and we think our results are better. Most of the patients in labor receive scopolamine hydrobromide, 0.32 mg. (1/200 grain) by hypodermic, and frequently it is repeated once. Usually we also give one dose of pentobarbital, 0.2 Gm. (3 grains), and most patients are also given Trilene if the above-stated medications do not make them comfortable. When the labor is long, we usually follow the scopolamine with Demerol, 50 mg., or Pantopon 0.01 Gm. (1/6 grain). Inhalation anesthesia of oxygen and ether or cyclopropane is most frequently used for the episiotomy and delivery of the baby. We do use spinal and local anesthesia in a fair number of cases.

TABLE IX. INDICATIONS FOR CESAREAN SECTION

Generally contracted pelvis	43
Flat pelvis	12
Funnel pelvis	8
Cephalopelvic disproportion	4
Former extensive vaginal plastic operation	2
Borderline pelvis, irregular fetal heartbeat	2
Former cesarean section, uterus didelphys	1
Former cesarean section	9
Double vagina and cervix, prolapsed cord	1
Uterine inertia	3
Cervical stenosis	1
Toxemia, eclampsia	1
Bicornuate uterus	1
Placenta previa	1
Uterine fibroids	1

TABLE X. FETAL AND INFANT MORTALITY, UNCORRECTED

	TOTAL NUMBER	PER CENT
Fetal deaths (stillbirths)	9	1.9
Infant deaths (neonatal deaths)	15	3.7
Combined fetal and infant deaths	24	5.7

TABLE XI. CAUSES OF FETAL AND INFANT DEATHS*

	NUMBER
Fetal Deaths.—	
Died in utero before labor	5
Died during labor, erythroblastosis fetalis	1
Died during labor, meningocele	1
Died during labor, hydrocephalus, craniotomy	1
Died during labor, cause unknown	1
Infant Deaths.—	
Multiple deformities	5
Atelectasis (3 maternal toxemia)	7
Intracranial hemorrhage	2
No cause found at autopsy	1

*Six, or 25 per cent, of the infants lost weighed less than 5 pounds, 8 ounces (2,500 grams).

TABLE XII. FETAL AND INFANT MORTALITY, CORRECTED*

	NUMBER	PER CENT
Fetal deaths (stillbirths)	1	0.21
Infant deaths (neonatal deaths)	9	1.9
Combined fetal and infant deaths	10	2.11

*This Table includes all fetal and infant deaths in cases where the babies had no congenital condition incompatible with survival regardless of the maternal complications.

The indications for cesarean section are shown in Table IX. Ten of the patients had previously been delivered by cesarean section, which gives an incidence of 16 per cent for primary cesarean sections in our patients with breech presentations. The incidence of cesarean section in our breech presentations during the past six years varied among the three doctors whose patients we are reporting. One member of the group delivered by cesarean section 8.5 per cent of all of his breech presentations.

Fig. 1.

Table X shows the uncorrected fetal and infant mortality. This includes all fetal and infant mortality in babies who weighed 1,814 grams (4 pounds) or more, regardless of the maternal complication or the condition of the baby at the onset of labor.

Table XI shows the causes of the fetal and infant deaths.

In Table XII the corrected fetal and infant mortality rates are shown. Prematurity was an important factor in these deaths.

Forceps to the aftercoming head were used 131 times in the 385 vaginal deliveries, an incidence of 34 per cent. We apply forceps to the head in vaginal breech deliveries only after the fetal head is engaged in the pelvis. A high forceps delivery of the head in a breech delivery is just as dangerous as it is in a vertex presentation. We prefer Piper forceps and they are put on the table for every vaginal breech delivery. We do not apply the forceps routinely, but we do use forceps whenever the head cannot be delivered easily by the Wigand-Martin maneuver.

Five mothers were given transfusions. Uterine packing was used in nine patients delivered vaginally.

We believe in the conservative management of the patient with a breech presentation. We induce labor on these patients only when there are definite indications and the patients have been carefully evaluated. In breech presentation, spontaneous rupture of the membranes before the onset of labor occurs frequently, but we try to avoid rupturing the membranes until the cervix is fully dilated and retracted and the breech is well engaged in the pelvis.

The patient with a breech presentation and ruptured membranes or in early labor must be watched closely and constantly. The fetal heart rate should be recorded frequently. This plan has enabled us to suspect or recognize a prolapse of the umbilical cord several times, and save the baby in each case.

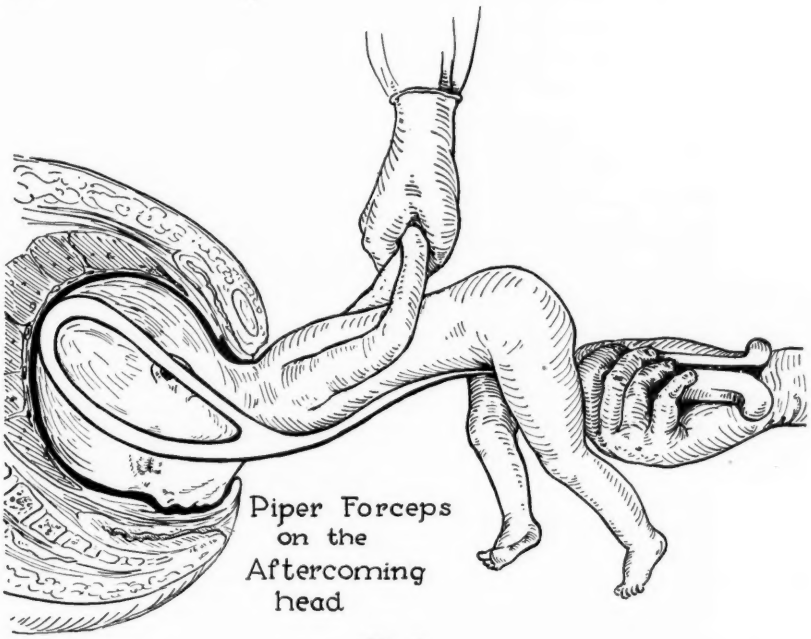

Fig. 2.

We believe that vaginal delivery of a breech presentation through an incompletely dilated and retracted cervix is dangerous and results in a high fetal mortality rate and frequent injury to the infant. We prefer to give our patients with breech presentations at least one hour or more in the second stage of labor before attempting a breech extraction. In the presence of fetal distress or maternal complications, this plan sometimes cannot be carried out.

We prefer the Potter method of breech extraction and we have found that it is usually easier to deliver the anterior shoulder first. Then, when the posterior shoulder is rotated anteriorly, it usually drops out or it can be delivered with less danger of trauma to the baby and mother. Gentleness and the avoidance of haste in delivering the shoulders and head will save many babies.

We wish to emphasize the importance of avoiding overextension of the baby's head during extraction. The relationship of the fetal head to the

body should remain throughout the extraction about the same as it is for the average individual in a walking position. The Piper forceps permit extraction of the head without overextension of the body. Overextension of the fetal head is a common cause of fracture of the baby's neck, just as undue traction on the baby's neck frequently causes nerve injury and paralysis.

Summary

We have reported 473 primary breech deliveries which occurred in 11,745 private patients delivered by three physicians since 1928, an incidence of 4.02 per cent for breech presentations in patients 28 weeks or more pregnant and infants weighing 1,814 grams (4 pounds) or more.

We recognize that external version of breech presentations should reduce the fetal and infant mortality associated with this complication, but we do not recommend the routine use of this procedure.

There was no maternal mortality. Eliminating infants who died before labor and those with congenital anomalies incompatible with survival, our corrected fetal and infant mortality rate for babies weighing 1,814 grams (4 pounds) or more or pregnancies of 28 weeks' or more duration was 2.11 per cent, and the uncorrected rate for all fetal and infant deaths was 5.7 per cent.

This rate of fetal and infant mortality is low by comparison with rates reported in the literature for infants of the same weight.

Breech presentation necessitates a careful evaluation of the maternal pelvis and the fetal size and position before the onset of labor whenever possible. X-ray studies frequently give valuable information in this type of presentation.

The total duration of labor in the vaginal deliveries was short as compared with that in other published reports. The average duration of labor for our primiparas was 10 hours and 57 minutes and for the multiparas the average was 8 hours and 48 minutes.

The baby was completely extracted in 15 per cent of the cases and some assistance, less than complete extraction, was given in 52 per cent of the cases.

We advise conservative treatment of patients with breech presentations whenever this plan can be followed. Labor should rarely be induced and it should not be hurried. A second stage of one or two hours will make extraction of the breech easier if it becomes necessary. In the presence of maternal or fetal distress, this plan cannot be followed.

Wide episiotomy should be used in most vaginal breech deliveries. No third-degree laceration occurred in any of our patients. We believe a wide episiotomy reduces trauma to both the mother and the baby.

We have found Potter's method of breech extraction most useful in our vaginal deliveries and we use it almost routinely.

In some cases, the Wigand-Martin maneuver for flexing and extracting the fetal head has been used most successfully. This maneuver is particularly useful when the fetal head is high in the pelvis and forceps should not be applied.

Piper forceps should be used whenever the fetal head is engaged in the pelvis and cannot be delivered easily by the Wigand-Martin maneuver.

Finally, a breech extraction should never be hurried and overextension of the fetal head must be carefully avoided.

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Discussion

DR. W. K. STROTHER, JR., Dallas, Texas.—To close observation and individualization of each patient may be accredited Dr. Ware's excellent salvage. The reporting of all maternal and fetal mortality as gross mortality and correcting by a stated plan gives a very accurate statistical report.

Our experience with external version has been very satisfactory. The procedure is attempted in all cases with the breech presenting within the last trimester. The frank breech group is less amenable to rotation than the footling group and is also associated with a smaller number of complications. With gentleness and frequent auscultation of the fetal heart, during attempted rotation, we have seen none of the serious complications described. If the original position is resumed version may be repeated until the cephalic position is maintained. This we do at weekly intervals.

We are in complete agreement with Dr. Ware as to the value of x-ray studies of these patients, both flat plate and pelvimetric studies. We do pelvimetric studies routinely on all primiparas and also on all multiparas with little known or questionable obstetrical histories. This latter group may be a source of trouble whether the presentation is cephalic or breech. From studying Table IX in the author's paper, i.e., "Indications for Cesarean Section," the value of pelvimetric studies as an adjunct in the determination of fetopelvic disproportion cannot be overemphasized. The broadening of the indications for cesarean section in this group, as well as the individualization of other cases, has decreased our maternal morbidity and fetal mortality materially.

The elderly primipara merits special consideration. This group accounts for a fair percentage of our cesarean section rate for breech presentation.

The management of breech delivery as outlined by the author has been more acceptable with us than the prophylactic "breaking up" of the breech. The patient is allowed to deliver the buttocks of the child herself and delivery is then completed under deep anesthesia with wide episiotomy and extraction. Potter's technique is employed for delivery of the shoulders. The importance of full dilatation and paralysis of the cervix

cannot be overemphasized. This has been accomplished at times with a foot presenting at the vulva by holding a vulval pad in place to prevent the leg from extruding from the vagina and to allow the buttocks to complete the dilatation. Delivery of the anterior shoulder is made much easier if extraction has exposed the scapula beneath the symphysis before the rotation of the shoulder girdle is begun. An attempt is always made to deliver the head and successfully so in the majority of cases by the Wigand-Martin maneuver. Piper forceps with the head well in the pelvis are used if any difficulty is encountered.

Analgesia has been reduced materially in the last few years, particularly in the latter part of labor. By this reduction, the length of the second stage has been shortened and the number of conversions and extractions diminished. The depressing effects of these drugs on premature infants must always be considered. Deep anesthesia is used for extraction, and delivery of the aftercoming head is accomplished slowly and deliberately.

Dr. Ware has presented a most concise evaluation of 473 primary breech deliveries. The close observation of these cases is evidenced by the fact that there were no fetal deaths in the twelve cases of prolapsed umbilical cords. Five and seven-tenths per cent is certainly an excellent gross fetal and infant mortality.

DR. JOHN E. SAVAGE, Baltimore, Md.—The authors report a series of 473 breech deliveries in 11,745 private patients, for an incidence of 4.02 per cent. We agree that gross mortality figures should be presented in the discussion of any complication of pregnancy. The authors have included fetal death in utero, anomalies, etc., in their gross perinatal mortality which was 5.7 per cent. Corrected gross fetal mortality was commendably low, being 2.11 per cent.

The routine employment of external cephalic version in breech presentation is a moot point. Success in this procedure depends somewhat upon one's enthusiasm for and experience with the technique.

We would make a plea for the use of the standard terms for describing types of breech delivery, viz., spontaneous breech delivery, partial breech extraction, and total breech extraction.

We believe that sterile pelvic examination is indicated to determine that the cervix is completely dilated and effaced before inducing anesthesia for breech delivery and especially before undertaking total breech extraction. We also believe it to be a helpful routine to have roentgen pelvimetry in all patients with breech presentation.

Although there were 12 instances of prolapsed cord, none of the babies were lost. This certainly speaks well for the operators' careful and skillful management. We are curious, however, as to when this complication arose in relation to cervical dilatation, since only one of these patients was delivered abdominally.

While the incidence of cesarean section in this series may seem somewhat high (total 18.6 per cent and primary 16.0 per cent), examination of the indications proves that the treatment was conservative. The incidence is definitely weighted by patients referred late in pregnancy or in labor, approximately 25 per cent being in this category.

We believe in the routine application of the Piper forceps to the engaged aftercoming head in term breech extraction. We teach this technique to house officers so that they may become thoroughly familiar with the instrument.

We do not pack the uterus. A prophylactic postpartum Pitocin drip (2 c.c. Pitocin in 1,000 c.c. 5 per cent glucose) given to patients delivered under general anesthesia will practically eliminate uterine atony. To rule out uterine rupture, we routinely palpate the interior of the uterus following total breech extraction.

In the absence of maternal or fetal distress, and under careful observation, we allow at least two hours of second stage labor before breech extraction is performed.

DR. NICKOLAS C. LOUROS, Athens, Greece.—On many points everybody agrees with Dr. Ware, but on some of them there might be different opinions—for instance,

on the way we manage primiparas and multiparas. These, I think, have to be treated differently. I usually apply the classic procedure in primiparas, but in multiparas I always use the excellent method of Bracht, which is based on the fact that one must never *pull* but always *push*. I think that the Kristeller principle plays a great part in the Bracht maneuver. We have good results with this method.

There is another point I would like to emphasize. Certainly anesthesia is always necessary in breech presentations. However, I want to report here on the influence of a procedure which I have called accelerated painless labor and which I have applied since 1946 as a routine. I have spoken on this subject on invitation at the Faculté de Médecine in Paris and at the Royal College of Obstetricians and Gynaecologists in London. This management of labor in general is a combination of sedatives and oxytocics. It is also important to inform the patient, if she is a primipara, how to expel the fetus. Then, when the cervix is completely dilated, the maneuver of Kristeller is applied, and when the head or even the breech appears at the vulva, a deeper anesthesia with nitrous oxide or Trilene is administered.

I am sorry I can't submit precise statistics showing the duration of labor and fetal mortality with this method, but I think they are slightly better than those presented by Dr. Ware. However, in primiparas with breech presentations we have an average duration of labor of 6 hours, while without this method the average duration is 16 hours and 30 minutes. In multiparas the average duration was 5 hours, 25 minutes instead of 8 hours, 45 minutes without the accelerated painless procedure. I am sorry I haven't with me the exact figures on fetal mortality in breech presentations, but I have the fetal mortality of all my cases (vertex and breech). In 6,963 cases where accelerated painless labor was applied, the total fetal mortality was 1.17, compared to 1.99 in cases where the method was not used.

One thing I would like to underline: I have never had to use forceps on the aftercoming head, because pushing by the Kristeller maneuver is always successful, and in my opinion much better than any pulling.

DR. JOHN PARKS, Washington, D. C.—Dr. Ware has referred to the increasing difficulties associated with breech delivery of large babies and to the increased incidence of babies presenting by breech weighing between 4 and 5½ pounds. I should like to mention a procedure of particular benefit to the premature infant presenting as a breech. These small infants, weighing from 4 to 5½ pounds, are big enough to survive, but often they die as the result of a traumatic passage through the birth canal. The smaller the infant, the larger the head is in proportion to the size of the body. It is the aftercoming head which presents a problem in delivery.

For several years we have been inserting a Voorhees bag into the uterus, preferably outside the membranes, when the cervix is effaced and 3 to 4 cm. dilated. The satisfactory expulsion of a well-inflated No. 6 bag prepares the birth passage and prevents constriction of the cervix and lower uterine segment about the small infant's aftercoming big head. This is a life-preserving procedure for premature infants, and it can be quite helpful even with the term fetus presenting as a footling or full breech. It is particularly applicable in the patient who has premature rupture of the membranes, a footling breech presentation, and who is not in labor. Bags are used so infrequently for other purposes today that in many hospitals one may not be available. However, we feel that bags should be preserved for this one emergency alone.

DR. ROBERT KIMBROUGH, Philadelphia, Pa.—I have enjoyed and have benefited greatly by Dr. Ware's excellent paper. I would like to commend him particularly on his not losing a single one of the 12 babies with prolapse of the cord. If time permits, I wish Dr. Ware would give us some information about the degree of cervical dilatation at the time prolapse occurred, and the principles of management that gave these excellent results, which are much better than we can achieve in Philadelphia. I would like to know also the incidence of placenta previa in this group.

I would like to pass on to this group a little trick that came up in my own practice during the past year. We have now used it in more than a dozen cases. I believe with Dr. Ware in the conservative management of breech deliveries. I prefer, under good analgesia, for the patient to put the breech in my hands with her own efforts. Formerly after the patient had put the breech in my hands with her own efforts, I would tell the anesthetist to get her under general inhalation anesthesia quickly; the patient squirmed and fought, and the drapes probably fell on the floor. To avoid this unfortunate sequence, we hit upon the idea of giving these patients intravenously a small dose of Pentothal Sodium as soon as the breech has been put in the operator's hands. The baby is so soon born that we have had no suggestion of narcosis, and absolute relaxation is given immediately when needed most.

DR. JOHN F. CUNNINGHAM, Dublin, Ireland.—There are just a few points which I would like to mention in connection with Dr. Ware's paper. First of all is the question of version in the treatment of breech. Now we in Dublin do practice version, prophylactic cephalic version, and there are one or two important points in connection with that procedure. First, you will find that nearly all breech presentations in primigravidas are extended. If you wait until the thirty-sixth week or later to attempt version in these cases it may be too late; you will then be unable to get the fetus around. Therefore we attempt version in these cases about the thirty-fourth week, and succeed in turning a great number of them. If the breech is not extended you can wait until much later, and, if it is not extended, a great number of them will turn spontaneously.

Another point is about anesthesia. We use general anesthesia, local anesthesia, or a combination of both. If we are about to do an extraction from the midpelvis or higher, of course a deep anesthetic is then necessary. That is purely an operative procedure, and the patient doesn't deliver the infant; the doctor does. But if the extraction is a low one or if the patient is having a spontaneous delivery, we give local anesthesia or light general anesthesia. It is very important that at that stage, and throughout that stage of the delivery, the patient's uterus should continue to contract. For that reason I have made it a practice for a number of years, when the perineum is well distended and the breech is appearing over the perineum, to give the patient 5 units of Pitocin. I have had no trouble with this; it does keep the uterus contracting, helps greatly in the delivery, and I have had no case of ruptured uterus. We have used sodium thiopentone also and we find it very useful. We use it also for low forceps delivery.

One last point concerns the delivery of the shoulders. I have followed Dr. Potter's method since he first described it many years ago, and I find that it is much easier and safer to deliver the anterior shoulder first. Dr. Potter then recommends that the body should be rotated so that the posterior shoulder becomes anterior. I have found this quite unnecessary. Once the anterior shoulder is delivered, the posterior arm and shoulder come out without the slightest difficulty, and I don't think that rotation should be done in these cases. I try to avoid rotation of the body and I like to teach my students to avoid it. I have seen too many cases of injury to the infant and damage to the vagina from forcible rotation of the body, and I think it is an unnecessary maneuver.

DR. MILTON POTTER, Buffalo, N. Y.—I would like to comment on the fact that even with complete effacement of the lower uterine segment, complete dilatation and deep anesthesia, our problems in breech extraction are not over. We must remember that the head is always unmolded; it is always extended, and we have no control of the arms.

I have been impressed also by the fact that the arms are not always where the teachers tell us they are. In breech extraction or in elective version and extraction, if the arms are not folded across the chest, you can expect trouble. Many times in breeches, as in other types of cases, the hand is alongside the head or alongside the body. Any attempt at extraction in a breech case of that nature with a normal-sized baby and a

normal-sized pelvis will result in death of the baby. Therefore, we must realize that in breech cases we have no control of the arms as we do in an elective version and extraction.

Dr. Edward Dennen some years ago pointed out to me the importance of using the head and shoulders of the fetus as the x-ray target on anterior and lateral flat plates to determine the position of the arms. If this technique does not show the arms in the folded position under the chin, then anybody who attempts an extraction in that case can expect a fetal death.

I don't agree with Dr. Ware in limiting cesarean sections for breech presentation to elderly primiparas. I think that any patient regardless of age, who has a normal-sized baby, is entitled to a cesarean when the fetal arms are not in the proper position. I feel also that it is important, as a previous speaker has mentioned, to push the head through the pelvis rather than to pull it through.

DR. WARE (Closing).—I have had no experience with the Bracht maneuver. In using the Martin-Wigand maneuver, the operator does make a fair amount of pressure on the fetal head with the hand on the abdomen above the symphysis, and with one or two fingers of the opposite hand you can make considerable traction on the lower jaw of the baby. This maneuver enables the operator to flex the baby's head and rotate it so as to place the largest diameters of the fetal head in the largest diameters of the mother's pelvis. It can be used when the head is high in the mother's pelvis and forceps should not be applied. We avoid traction on the baby's shoulders particularly, because we think it increases the danger of paralysis in the baby. The head can be delivered with much less trauma by traction on the lower jaw or with Piper forceps.

The classification for delivering breech presentations as outlined by Dr. Savage has some advantage over the one we used, but either classification includes the three types of vaginal delivery and our deliveries can be classified as no assistance, partial assistance, and complete extraction.

We prefer to use local or spinal anesthesia when the baby seems to be premature or small, because we think this gives the premature babies a better chance. We have not used intravenous anesthesia for any of these deliveries.

There is a certain element of luck in everything, and, fortunately, the patients with prolapse of the umbilical cord were being watched closely. One patient with a prolapse was delivered by cesarean section because the cervix was dilated only 2 to 3 cm. Two others were multiparas, and the babies were small and did not cause much pressure on the cord. The others had complete cervical dilatation and were delivered fairly quickly. Prolapse of the cord occurs most frequently in footling presentations.

Only one patient had placenta previa and six patients had premature separation of the placenta.

SOME RECENT OBSERVATIONS CONCERNING THE TOXEMIAS OF PREGNANCY*

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(From the Department of Obstetrics of the State University of New York Medical Center at Syracuse, N. Y.)

THE toxemias of pregnancy, namely, pre-eclampsia and eclampsia, are distinct clinical entities associated only with pregnancy. Although there are many unusual physiological and chemical changes which occur in the body when these pregnancy complications occur, the most significant finding is generalized edema. The cause of such edema has generally been attributed to the retention of sodium chloride. Dieckmann[1] has demonstrated that pregnant patients with pre-eclampsia and eclampsia are not able satisfactorily to concentrate sodium and chloride ions in the urine. He has also demonstrated in these patients that there is a delayed elimination of sodium chloride after a test dose of this material and has likewise reported that intravenous injection of a solution of sodium chloride in toxic patients on two or more consecutive days has caused an increase in blood pressure and weight and has even created symptoms suggestive of imminent eclampsia. Others have reported similar findings in these pregnancy complications.

The many physiologic processes involved in the metabolism of sodium chloride and water in the nonpregnant individual are made more complex by the addition of a fetus with its placenta within the body. The intake of salt and water, the ability of the kidneys to eliminate and reabsorb these materials, and the effect of the secretion of the endocrine glands upon these functions seem to be some of the important factors in maintaining the fluid balance within the body. It is the purpose of this presentation to discuss the relationship of these problems in normal and toxemic pregnancy.

The importance of the action of hormonal substances upon the metabolism of salt and water has been described and emphasized many times before. For example, certain steroids of the adrenal cortex, working through the kidney, assist in and are necessary for normal excretion of salt and water.[2] In general these steroids tend to cause water excretion and salt retention. The relative amounts of these responses are dependent upon the structure of the steroids. On the other hand, the hormones from the posterior lobe of the pituitary gland designated as antidiuretic substance cause water retention and usually sodium and chloride excretion. A reciprocal relationship between these hor-

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mones has been proposed previously.[3] Many studies concerning the role of antidiuretic substance in the toxemias of pregnancy have been reported, especially since the suggestion of Hofbauer[4] on theoretical grounds that the posterior pituitary hormones might play a part in the development of eclampsia, and since the report of Anselmino, Hoffmann, and Kennedy[5] of an increased level of an antidiuretic material in the plasma of toxemic patients. Certain studies[6-11] have failed to demonstrate an antidiuretic substance in these conditions, while others[12-14] have failed to show a correlation between antidiuretic activity and toxemia of late pregnancy. Some reporters[15-18] have been able to show an increased antidiuretic activity or an increased sensitivity to exogenous posterior pituitary hormone in patients with pre-eclampsia and eclampsia. Venning,[19] Tobian,[20] Devis,[21] and Jailer[22] have reported concerning the adrenal corticosteroid excretion during normal and toxemic pregnancy and have found the levels of these steroids to be increased in toxemia. No simultaneous studies of antidiuretic and adrenal cortical substance during pregnancy have been made. Therefore, it was thought pertinent to study the relationship of these factors to the metabolism of salt and water in normal and toxemic pregnancy. Because pregnandiol and chorionic gonadotrophin excretion were also altered during toxemia, it was felt worth while to attempt to correlate the urinary excretion of these materials with the other measurements.[23-27]

Plan of Endocrine Study

The urinary excretion of chorionic gonadotrophin and pregnandiol was calculated in 75 normal pregnant patients from the beginning of gestation until term. These studies together with the estimation of the excretion of total adrenal cortical steroids and antidiuretic substances were completed in 7 of these normal pregnant patients and also in 11 patients who developed pre-eclampsia and eclampsia in the latter months of gestation. Twenty-four hour specimens of urine were collected from these women at approximately two-week intervals. At the conclusion of each collection period a specimen of venous blood was drawn and serum antidiuretic activity was estimated within 30 minutes after the blood was taken. These measurements were carried out as frequently as possible in patients with toxemia of pregnancy. Since the completion of this study, excretion of total adrenal corticosteroids has been under way in 3 additional normal women and in 21 patients who have developed toxemia. Though the work has not been completely finished, trends seem to be comparable to those in the studies completed and here reported.

Methods

Twenty-four hour urine specimens were refrigerated during collection or when refrigeration was impossible chloroform was added as a preservative. All the determinations were carried out as soon as possible at the completion of the collection, usually within 2 or 3 hours. Pregnandiol was measured by the method of Guterman and Schroeder.[28] Chorionic gonadotrophin was measured by the method of Behnken, Lloyd, and Hughes.[29] For this method, 1 rat unit equals from 2½ to 3 international units of chorionic gonadotrophin. Corticosteroids were determined by the method of Lloyd and Lobotsky.[30] The "total corticosteroid" excretion was measured for all specimens. The corticosteroids were further differentiated by determining the "freely water-soluble"

ones, and the "poorly water-soluble" ones. In almost all of the nonpregnant women, the former group of steroids is essentially equivalent to the total corticosteroid excretion and a very little of the latter group has been found. The formaldehyde formed is converted to milligrams of corticosteroid by multiplication by a factor of 11.5.[31] The normal range of values in the nonpregnant women of the same age as those studied in this series is from 0.20 mg. to 0.75 mg. per 24 hours, averaging 0.42 mg. per 24 hours.

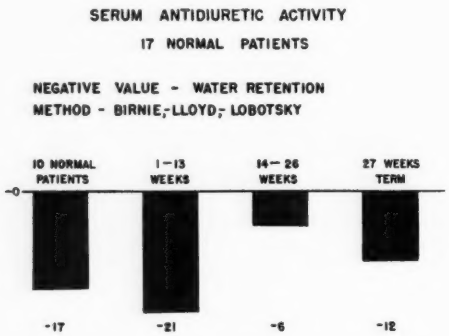

Fig. 1.—Graphic demonstration of the ADS activity in nonpregnant and normal pregnant patients.

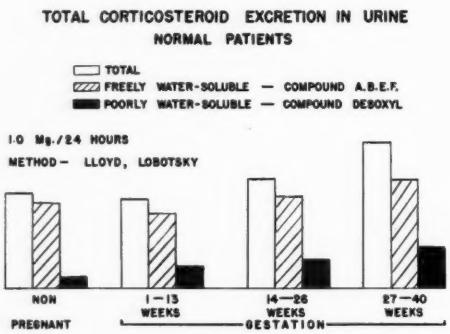

Fig. 2.—Graphic demonstration of the increased excretion of the total, freely water-soluble and poorly water-soluble adrenal corticosteroids.

The serum antidiuretic activity, ADS, was estimated by a modification of the method of Birnie and his associates,[32] described by Lloyd and Lobotsky.[23] The antidiuretic activity was expressed in the following way: The percentages of water load excreted at the end of a 90-minute period by rats that have been injected with the serum being assayed or physiological saline solution were calculated. The difference between these percentages represented the antidiuretic activity. The antidiuretic activity was expressed as a negative value when the serum of patients caused the rats used as test animals to retain water; whereas, it was expressed as a positive value when it caused the animals to excrete water. In a series of 39 determinations carried out on 5 normal men and 5 normal women an average antidiuretic activity of −17 for each sex was found with a range of from −41 to +13.

Specimens of urine from normal and toxemic patients have been subjected to chromatographic separation of adrenal steroids by a modification of Zaffaroni, Burton, and Keutmann,[33] using a benzene formamide solvent system

on paper. By this method, the major position of the steroids excreted by the nonpregnant individual moved at the rate characteristic of steroids containing 5 oxygen atoms; a lesser amount of steroids has been found at a rate of flow similar to those containing 4 oxygen atoms.

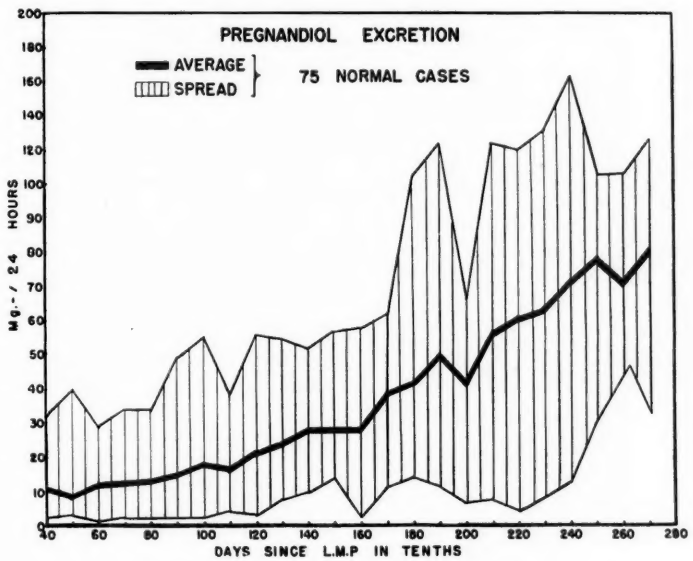

Fig. 3.—Note the gradual increase in the excretion of pregnandiol until term.

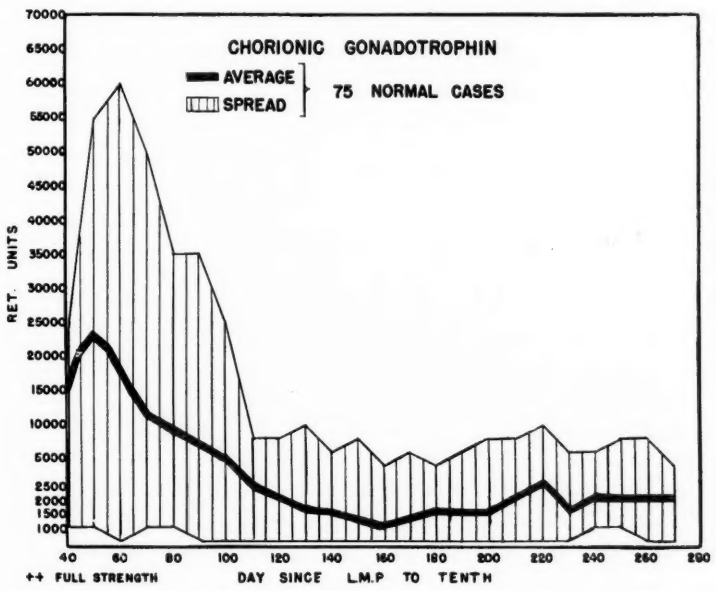

Fig. 4.—Note that the excretion of chorionic gonadotrophin reaches a peak from the sixtieth to seventieth day of gestation, remaining at a constantly low level throughout the pregnancy.

Results

Normal Pregnancy.—

The findings for normal pregnancy are summarized in Tables I and II. Pregnancy has been divided roughly into three trimesters. The last trimester has been considered as beginning at the twenty-seventh week to permit a closer comparison of the patients with toxemia, all of whom were in the twenty-seventh week of pregnancy or later.

Serum antidiuretic activity: There was no difference in antidiuretic activity of serum between any of the three trimesters of pregnancy and no difference between the pregnant and the nonpregnant women (Fig. 1).

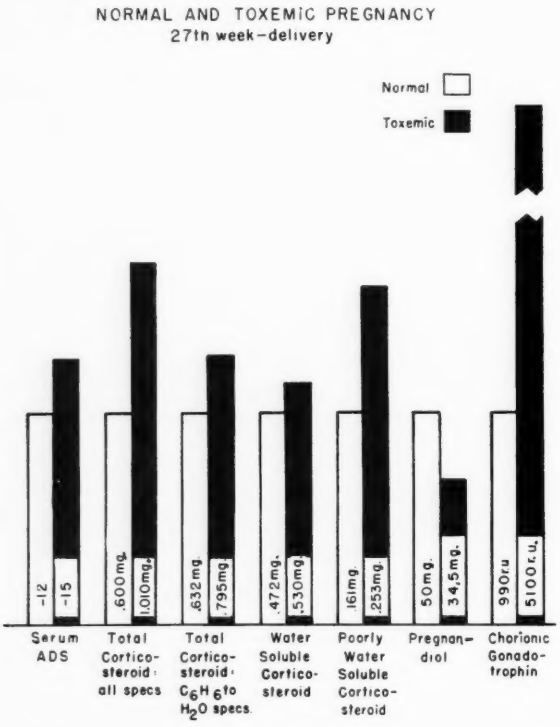

Fig. 5.—Comparison between the excretion of hormones in normal and toxemic pregnancy.

Excretion of "total corticosteroid": Excretion of "total corticosteroid" increased during pregnancy, with an average during the last trimester which is near the upper limit of the normal range for nonpregnant women. During this trimester, many normal pregnant patients excreted amounts of corticosteroid considerably above the normal nonpregnant range (Fig. 2).

Excretion of "freely water-soluble" and "poorly water-soluble corticosteroid": During the first trimester almost all of the "total corticosteroid" was water soluble. During the second and third trimesters, an appreciable amount of corticosteroid that did not pass from benzene into water was present. During the third trimester, approximately 25 per cent of the "total corticosteroid" was poorly soluble in water.

Excretion of pregnandiol: An increase in pregnandiol excretion occurred throughout pregnancy, reaching a peak just before delivery (Fig. 3).

Excretion of chorionic gonadotrophin: The urinary chorionic gonadotrophin level was highest during the first trimester, subsequently falling and remaining at a low level throughout the rest of pregnancy (Fig. 4).

TABLE I. THE SERUM ANTIDIURETIC ACTIVITY, TOTAL CORTICOSTEROID, PREGNANDIOL, AND CHORIONIC GONADOTROPHIN LEVELS IN NORMAL PREGNANCY

TYPE AND NUMBER OF SUBJECTS	SERUM ANTIDIURETIC ACTIVITY		TOTAL CORTICOSTEROID MG./24 HOURS		PREGNANDIOL MG./24 HOURS		CHORIONIC GONADOTROPHIN R.U./24 HOURS	
	NUMBER OF SAMPLES	MEAN ± S.E.*	NUMBER OF SAMPLES	MEAN ± S.E.	NUMBER OF SAMPLES	MEAN ± S.E.	NUMBER OF SAMPLES	MEAN ± S.E.
Nonpregnant (10 subjects)	39	−17 ± 1.9	64 (31 subjects)	.420 ± .016				
1-13 weeks' pregnancy (3 subjects)	6	−21 ± 5.5	7	.400 ± .052	10	12.2 ± 2.2	13	10,300 ± 1,410
14-26 weeks' pregnancy (5 subjects)	18	−6 ± 3.5	21	.496 ± .026	19	30.4 ± 3.7	21	855 ± 200
27th week delivery, pregnancy (6 subjects)	15	−12 ± 3.8	22	.600 ± .036	14	50.1 ± 8.4	27	990 ± 128

*S.E. = standard error.

TABLE II. NORMAL PREGNANCY—SPECIMENS ON WHICH BENZENE TO WATER PARTITIONS OF CORTICOSTEROIDS WERE PERFORMED

TYPE AND NUMBER OF SUBJECTS	TOTAL CORTICOSTEROID MG./24 HOURS		FREELY WATER-SOLUBLE CORTICOSTEROID MG./24 HOURS		POORLY WATER-SOLUBLE CORTICOSTEROID MG./24 HOURS	
	NUMBER OF SAMPLES	MEAN ± S.E.	NUMBER OF SAMPLES	MEAN ± S.E.	NUMBER OF SAMPLES	MEAN ± S.E.
Nonpregnant (13 subjects)	22	.419 ± .029	22	.386 ± .028	22	.054 ± .016
1-13 weeks' pregnancy (3 subjects)	6	.393 ± .061	6	.330 ± .064	6	.070 ± .034
14-26 weeks' pregnancy (5 subjects)	20	.496 ± .026	20	.375 ± .024	20	.107 ± .015
27th week delivery, pregnancy (6 subjects)	20	.633 ± .037	20	.472 ± .032	20	.161 ± .024

Patients With Toxemia of Late Pregnancy.—

Eleven patients with pre-eclamptic toxemia were studied. All these patients were in the twenty-seventh week of pregnancy or later. These studies are summarized in Tables III and IV. A comparison of the values of normal pregnancy and of pre-eclamptic toxemia is shown in Fig. 5.

TABLE III. THE SERUM ANTIDIURETIC ACTIVITY, TOTAL CORTICOSTEROID, PREGNANDIOL, AND CHORIONIC GONADOTROPHIN LEVELS IN TOXEMIA OF PREGNANCY

TYPE AND NUMBER OF SUBJECTS	SERUM ANTIDIURETIC ACTIVITY		TOTAL CORTICOSTEROID MG./24 HOURS		PREGNANDIOL MG./24 HOURS		CHORIONIC GONADOTROPHIN R.U./24 HOURS	
	NUMBER OF SAMPLES	MEAN ± S.E.	NUMBER OF SAMPLES	MEAN ± S.E.	NUMBER OF SAMPLES	MEAN ± S.E.	NUMBER OF SAMPLES	MEAN ± S.E.
All cases of toxemia (11 subjects)	18	−15 ± 3.9*	25	1.010 ± 0.204†	19	34.5 ± 5.9	39	5,130 ± 850
Severe toxemia (6 subjects)	12	−17 ± 4.9	10	1.635 ± 1.27‡	14	34.8 ± 7.3	27	6,320 ± 1,190
Moderate and mild toxemia (5 subjects)	6	−10.5 ± 5.5	15	.700 ± 0.067	5	34 ± 12.5	12	3,683 ± 960

*The difference between this value and the average serum antidiuretic activity of all normal pregnancies (27th week to term) is not significant. $t = 1.7$, $p = .1$.

†The difference between this value and the average total corticosteroid of all normal pregnancies (27th week to term) is not statistically significant. $t = 1.65$, $p = >.1$.

‡The difference between this value and the average total corticosteroid of all normal pregnancies (27th week to term) is highly significant. $t = 3.5$, $p = <.01$.

TABLE IV. TOXEMIA CASES IN WHICH BENZENE TO WATER PARTITIONS OF CORTICOSTEROIDS WERE PERFORMED

TYPE AND NUMBER OF SUBJECTS	TOTAL CORTICOSTEROID MG./24 HOURS		FREELY WATER-SOLUBLE CORTICOSTEROID MG./24 HOURS		POORLY WATER-SOLUBLE CORTICOSTEROID MG./24 HOURS	
	NUMBER OF SAMPLES	MEAN ± S.E.	NUMBER OF SAMPLES	MEAN ± S.E.	NUMBER OF SAMPLES	MEAN ± S.E.
All cases of toxemia (11 subjects)	19	.795 ± .105	19	.530 ± .083	19	*.253 ± .136
Severe toxemia (6 subjects)	5	1.200 ± .109	5	.800 ± .26	5	†.390 ± .170
Moderate and mild toxemia (5 subjects)	14	.680 ± .068	14	.435 ± .05	14	.210 ± .033

*The difference between this value and the average poorly water-soluble corticosteroid of all normal pregnancies (27th week to term) is not significant. $t = 1.91$, $p = >.05<0.1$.

†The difference between this value and the average poorly water-soluble corticosteroid of all normal pregnancies (27th week to term) is probably significant. $t = 2.5$, $p = >.01<.02$.

Serum antidiuretic activity: The average of the 18 determinations was −15. The range of these values was large and the difference between the activity of the patients with pre-eclamptic toxemia and the normal pregnant women was not statistically significant.

Excretion of "total corticosteroid": The 25 determinations on specimens from the 11 patients showed an average of 1.010 mg. of corticosteroid in 24 hours with a range of from 0.265 mg. to 4.750 mg. per 24 hours. This average was 61 per cent higher than the average for the third trimester of normal pregnancy.

Excretion of "freely water-soluble" and "poorly water-soluble corticosteroid": In addition to the "total corticosteroid" determination, benzene to water partitions were carried out on 19 specimens collected from patients with

pre-eclamptic toxemia. The average "total corticosteroid" for these 19 specimens was 0.795 mg. per 24 hours. Of this corticosteroid 0.530 mg. was "freely water-soluble" and 0.532 mg. was "poorly water-soluble."

Excretion of pregnandiol: The average value of pregnandiol of 19 twenty-four hour specimens was 34.5 mg., which is considerably lower than the average for the normal subjects.

Excretion of chorionic gonadotrophin: A total of 39 measurements were carried out on specimens from the 11 patients with toxemia. The average excretion was 5,130 R.U. for 24 hours, which was over five times as high as the average for normal pregnancy.

Comparison of Mild and Severe Pre-eclampsia.—

The 11 patients with toxemia were divided into six "severe" cases, one "moderate" case, and four "mild" cases of pre-eclampsia. This purely arbitrary division of cases was made without knowledge of the antidiuretic activity or corticosteroid values of the patients. Those patients with "severe" eclampsia had higher corticosteroid excretion, larger amounts of "poorly water-soluble corticosteroid," and higher chorionic gonadotrophin excretion than are found in the patients with "moderate" or "mild" toxemia, although the number of determinations is insufficient to be statistically significant. The moderate or mild toxemia patients showed little, if any, deviation of the values from the normal range. Excretion of the adrenal steroid and placental steroid followed this pattern in the other cases now under study.

Fractionation by Paper Chromatography of Urinary Corticosteroid.—

The significance of the increased "poorly water-soluble" material which is found in the last trimester of pregnancy and which is further increased in toxemias is at present unknown. Several urine specimens of these patients have been studied by paper chromatography in an attempt to identify this material further. A fraction has been noted in the residue of toxic patients which appears on paper to move more rapidly than desoxycorticosterone. Another alpha-ketol which moves more rapidly than corticosterone has also been observed. A small amount of this similar material was found in some of the normal patients, but there was a significantly increased amount noted in those with severe toxemia. Although we realize that registering this material in this position chromatographically on paper does not identify the true structure of these steroids, it does suggest that there may be a substance present in the normal and especially in the toxic patient resembling the desoxyl group of adrenal steroids and which may have similar salt-retaining power. Other workers have found a material apparently quite similar in nature in toxic patients by using other methods of detection. For instance, Chart, Shipley, and Gordon[34] have evidence suggesting increased amounts of a salt-retaining material in the urine of toxemic patients. Likewise, Venning and her associates[35] have measured formaldehyde-forming corticosteroids and glycogen-depositing corticosteroids in women with toxemia. They have found that there is a greater amount of the formaldehyde-forming material which

does not cause glycogen deposition in toxic patients. Therefore, as evidence accumulates, it seems quite possible that there is excreted in the urine a salt-retaining substance in the normally pregnant patient in a lesser degree and statistically in greater amounts in toxic women.

Relationship to the General Metabolism of the Body.—

Although no definite conclusion can be drawn from this small series of cases, it is statistically significant that there is an increased excretion of the adrenal corticosteroids together with the placental hormones during normal gestation. Because the increased amounts of these substances occur about the same time of gestation that the maternal structure is undergoing a marked increase in its general metabolism, it seems proper to assume that these responses are intricately related. This mass cellular activity, affecting every organ in the body, is elicited by a rather drastic surge of energy. Clinically,

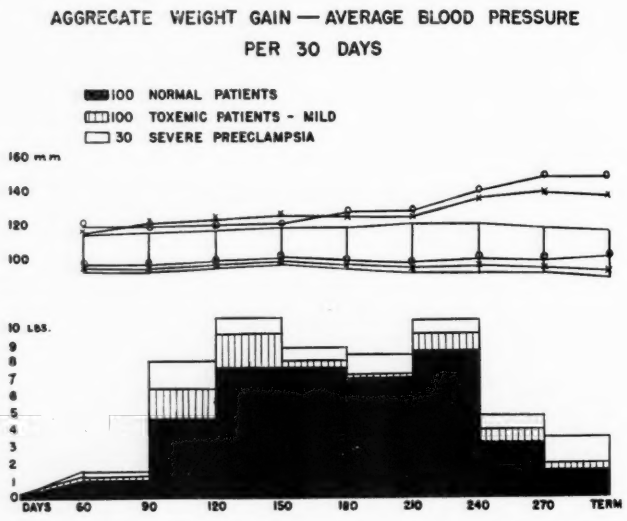

Fig. 6.—Note that the greatest aggregate weight gain in normal and toxic patients occurred between the ninetieth to one hundred fiftieth and the two hundred tenth to two hundred fortieth days of gestation. All patients were placed on low intake of sodium chloride at the sixth month.

this surge seems to stimulate all functions of the body, causes a feeling of well-being, and creates a considerable increase in the appetite. Careful questioning of patients revealed that there is added desire to ingest larger quantities of salt and to drink more water at this time. Those observations were further demonstrated in animals. Although it is apparent that a certain amount of maternal weight gain is due to fetal and placental size, we are convinced that a greater percentage of the actual weight gain during the last two trimesters is due to the retention of water created by an increased storage of sodium chloride. This storage of sodium chloride in the latter portion of gestation is a part of the increased output of the "poorly water-soluble" adrenal steroids. In toxemia, this relationship becomes even more suggestive. Dieckmann[1] and Chesley have also correlated the weight gain and retention of sodium chloride.

Careful recording of the aggregate weight gain every 30 days during 100 normal and 100 toxemic pregnancies demonstrated some of these relationships. The records were taken from our present files and were chosen at random. The toxic group were not severely affected, as noted by the blood pressure changes and other clinical findings. In both series, the bulk of the weight gain occurred between the ninetieth and two hundred tenth days. The toxic patients started to gain at the ninetieth day of gestation and the amount of deposition was greater even at this early period. All patients were placed upon a low sodium chloride and water intake at the sixth month. This restriction was reflected in the loss of weight. Thirty patients were selected from the group of 100 toxic women because they represented the more severe type of toxemia, although even these were not extremely toxic. The same pattern of weight gain was observed except the amounts were again increased over the normal and the other group of toxic individuals (Fig. 6). The weight patterns were compared in 15 women who were normal in the first

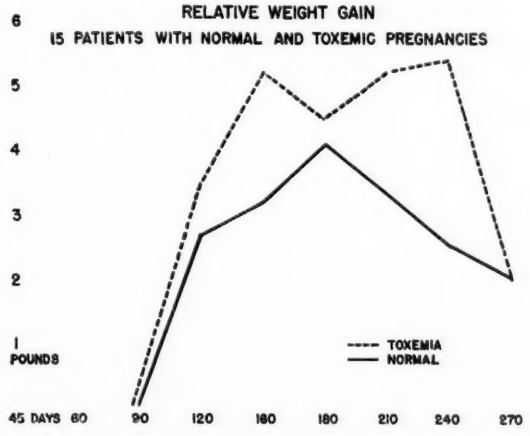

Fig. 7.—Weight gain relationship in the same patient in normal and toxemic pregnancy is similar to the gain noted in Fig. 6.

trimester of pregnancy, but who were toxic in the second (Fig. 7). Again this same pattern was noted with the weight starting to accumulate in significant amounts as early as the one hundred fiftieth day of gestation.

Relationship to the Kidney.—

Although these hormones may be involved in the general metabolism of the body, their continued influence upon the maternal kidney over a period of months may eventually affect its function. The total 24 hour urine volume was estimated in the 75 women who brought their urine to the laboratory for hormonal assay. The total output was decreased as pregnancy advanced. There were no restrictions on these patients to decrease the excretion. In creating this condition, the adrenal steroids may affect the tubules of the kidney so that sodium chloride is either more completely or perhaps more rapidly reabsorbed by this structure. This process, no doubt, is carried on during normal pregnancy without further difficulty. The prolonged action

of these steroids upon the kidneys may sensitize them to other toxic substances and increase the possibility of toxemia of pregnancy. Masson, Corcoran, and Page[36] and Gaunt[37] have reported the prolonged effect of desoxycorticosterone and sodium chloride upon the kidney in rats. Studies of the kidneys in these animals showed changes quite typical of those noted in eclamptic patients. These animals, however, did not develop the eclamptogenic syndrome. These workers have reported the following changes in the kidneys after this type of therapy: "The kidneys were enlarged, pale, irregular and spotted with an occasional flea bite hemorrhage. Microscopically, the kidney showed tubular dilatation and glandular hyaline casts. The glomeruli were enlarged. The epithelial cells were proliferative and swollen, resulting in partial or complete obliteration of some of the capillaries. Synechiae were found between the tufts in the capillary membranes." They further have produced the eclamptic syndrome in animals treated with renin after they were made hypertensive with implantation of pellets of desoxycorticosterone and maintained on 1 per cent sodium chloride for a period of 30 days.[38, 39]

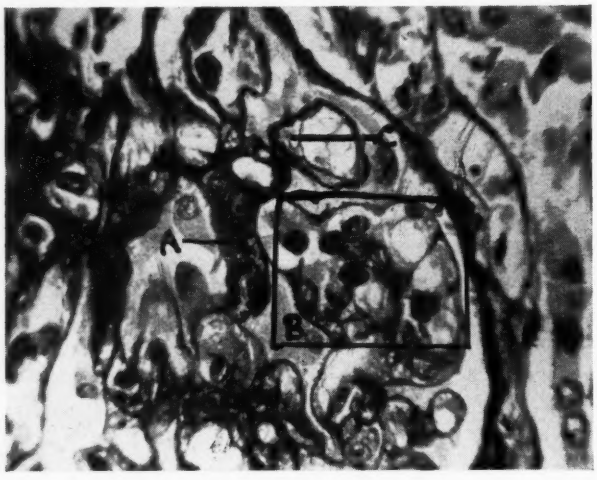

Fig. 8.—Section of glomerulus adjacent to Bowman's capsule near ruled square. *A*, Connective stalk by which capillaries are supported. *B*, Ruled square shows swollen capillary with edema in connective tissue around individual capillaries. *C*, Edema between basement membrane of capillary and epithelial covering.

Jones[40] of the Pathological Department of our Center has reported very similar changes in the human eclamptic kidneys. With a McManus PAS stain or a periodic acid silver methenamine stain he has shown that the swollen glomeruli with narrowed capillaries seen in eclampsia result from the accumulation of fluid in the connective tissue spaces of the glomerulus. He has demonstrated that each capillary of the glomerular tuft has two basement membranes with a potential connective-tissue space between them. The inner basement membrane is related to the endothelial cell and the outer basement membrane to the epithelial cells of the tuft. Normally, these two membranes appear as one (Fig. 8), but, with the accumulation of fluid in the connective-tissue space between them in eclampsia, their duality is readily seen. This

fluid causes swelling of the glomerular tufts and later of the glomeruli themselves. It seems to be homogeneous in character with a slightly fibrillar appearance, but does not contain inflammatory cells of any type. On this basis, it appears to be more of a transudate than an exudate. The lack of inflammatory cells would differentiate it from the fluid exudate noted in acute glomerular nephritis which also appears in the same area. Relatively nonspecific findings in the epithelium of the tubular apparatus have also been noted in these patients.

These pathological changes, which are either a part of the generalized edema of the body or the result of the prolonged action of the increasing amount of the "poorly water-soluble" steroids, may influence the function of the kidney in several ways. This fluid may encroach upon the vessels of the capillary tufts, gradually decreasing the size and eventually interfering with the blood flow through them. It may also obstruct the drainage of lymph from these areas. The filtration of fluid from the capillary to Bowman's capsule may also be diminished. All of these factors may temporarily influence the kidney function during the toxemias of pregnancy. Various workers have observed that the filtration rate is not appreciably interfered with in toxemia at the height of the disease. The rather rapid disappearance of fluid from the body and probably from the kidney could account for the rather prompt return of kidney function to normal in these patients soon after delivery. The disappearance of this fluid seems to be synchronous with the rapid decrease of hormonal substance which occurs when the patient is delivered.

Comment

It is quite apparent that the maternal structure is under the influence of increasing amounts of hormones during normal gestation and particularly during toxemic pregnancy. As a result of these hormonal changes, the body undergoes a rather drastic physiological activity. During the first trimester the important hormone seems to be chorionic gonadotrophin from the Langhans cells of the trophoblast. The action of this material appears to be a local one upon the corpus luteum stimulating it to prolong its secretion of estrogen and progesterone. These hormones react upon the decidua increasing its vascularity and producing nutritive substances necessary for early ovular growth. There is only a moderate effect upon the general metabolism of the body at this time. During the second and third trimesters, the important hormones are estrogen and progesterone which are now secreted by the placenta and which are thrown into the maternal circulation in rather enormous quantities. The increased secretion of adrenal corticosteroids together with the combined action of the placental steroids may create the increased cellular activity which takes place in the body as the pregnancy advances. These physiological alterations seem to describe an attempt on the part of the maternal organism to provide an overabundance of nutritive material to assure adequate fetal growth while in utero. It is no wonder that the increased amounts of poorly water-soluble material perhaps may increase the desire for salt ingestion and cause retention of this material at the same time. In

most instances the body can stand this marked physiological increment without difficulty. However, in susceptible individuals added stress or strain such as poor nutritional status, infections, or climatic disturbances might narrow the margin of safety and throw this process off balance.

Fig. 9.

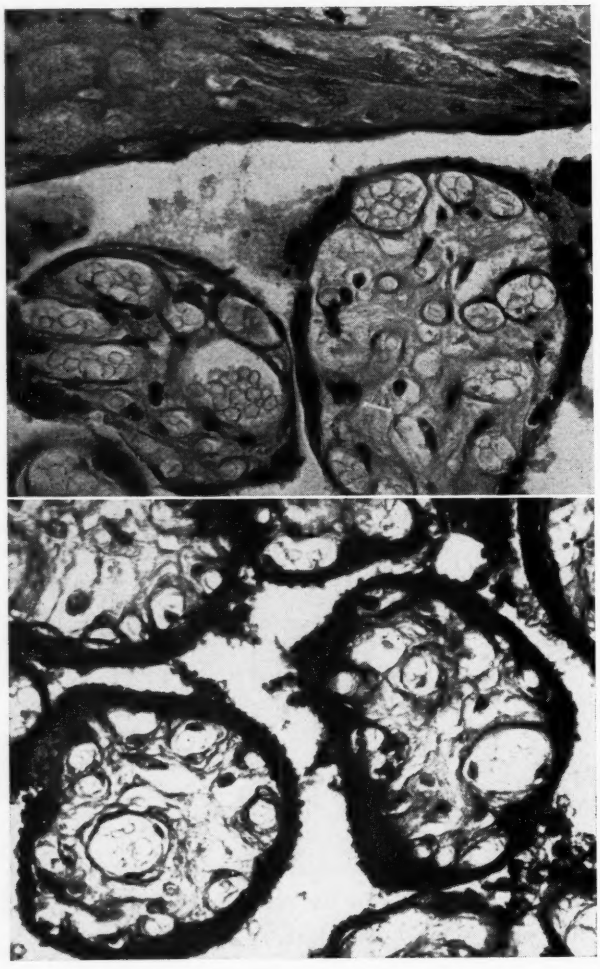

Fig. 10.

Fig. 9.—Placenta. Normal chorionic villi and decidua (bottom of picture). No glycogen-staining material present. (Glycogen stain. ×600; reduced ⅓.)

Fig. 10.—Term placenta. Note large quantities of alkaline phosphatase in the syncytial cells of the villi. (Alkaline phosphatase stain. ×600; reduced ⅓.)

It is certain that neither the increased amounts of these hormones nor the increased cellular activity alone or together can create pre-eclampsia or eclampsia. It seems that there must be some additional factor involving other systems which must set off a cycle of events characterized by the toxemias of pregnancy.

The placenta, which is probably responsible for the stimulation of the bodily metabolism by its increased production of estrogen and progesterone,

may provide the added unknown factor which changes the normal into the abnormal. Degenerative changes in this structure are manifested hormonologically by: (a) the increased levels of estrogen and progesterone, (b) increased levels of chorionic gonadotrophin. They are observed pathologically by: (a) edema of the chorionic villi, (b) sclerosis of the vessels of the villi, (c) fibrinoid degeneration in and about the villi. These changes may produce

Fig. 11.

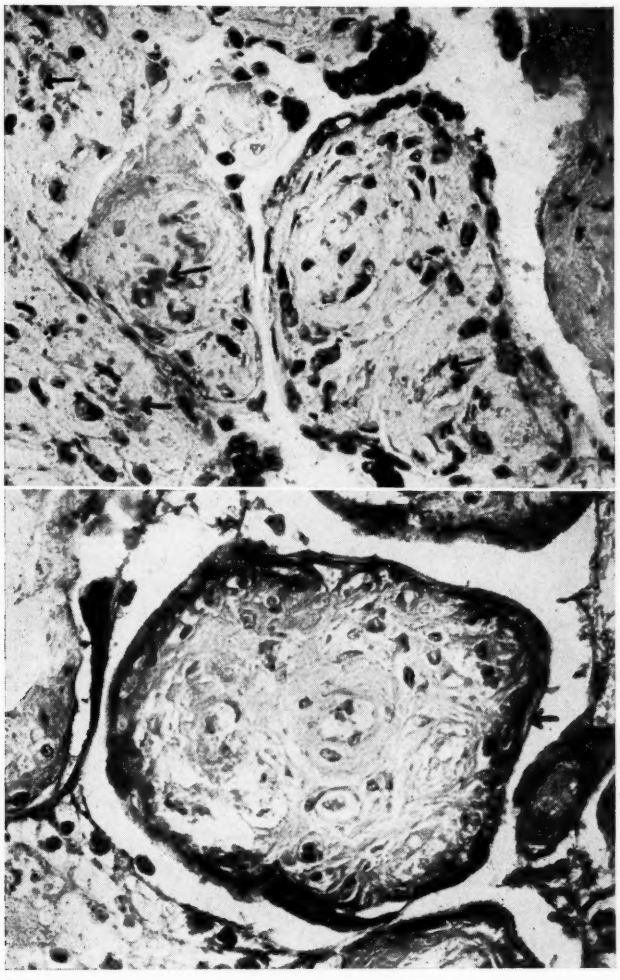

Fig. 12.

Fig. 11.—Term placenta of toxic patient. Note black-appearing granules in the substance of the villi. (Glycogen stain. ×660; reduced ⅓.)

Fig. 12.—Same placenta as shown in Fig. 11. Note diminished amount of alkaline phosphatase in the syncytium. Compare with Fig. 10. (Alkaline phosphatase stain. ×575; reduced ⅓.)

an enzyme or similar substance which may affect the kidneys and the body in an adverse manner. These decreasing levels of estrogen and progesterone and the increasing levels of chorionic gonadotrophin are significant of failing placental physiology. All of these alterations are found when toxemia of

pregnancy is developed. We have noted other changes in the placenta in respect to placental physiology which lend support to this possibility. During the early months of gestation, for instance, sugar is stored in the chorion because the principal function of the fetal liver at that time is to produce blood rather than to carry on the process of glycogenesis. During the latter portion of pregnancy, however, the chorion no longer stores sugar and is rich in alkaline phosphatase (Figs. 9 and 10). The fetal liver now assumes the process of normal glycogenesis—metabolizes and stores sugar as glycogen. In pre-eclampsia and eclampsia, the placenta again starts to store a glycogen-staining substance (Figs. 11 and 12) and the amount of alkaline phosphatase is diminished in the placenta. These processes have been observed by histochemical methods in respect to the chorion and normal placenta, and have been reported chemically by Villee.[41, 42] Perhaps this reversal denotes altered function of the liver, a disturbed enzyme system of the placenta, or is characteristic of degenerative changes of the placenta. The true meaning of these observations remains speculative. In any respect, it brings to our attention that placental and fetal relationships must be further clarified in respect to the toxemias of pregnancy, and more complete studies of the placenta are indicated.

Summary

1. There is no increase in antidiuretic activity of serum during normal and toxemic pregnancy.

2. "Total corticosteroid" increases throughout pregnancy, reaching a peak before delivery. Freely water-soluble corticosteroid increases throughout pregnancy. A poorly water-soluble material appears during the first trimester and increases until the end of pregnancy, constituting 25 per cent of the corticosteroid.

3. In toxemia, corticosteroid is considerably increased above the level found in normal pregnant women at the same stage of pregnancy. The poorly water-soluble component is also considerably increased above that seen in the normal, respresenting approximately 35 per cent of the total corticosteroid. In one patient with eclampsia, paper chromatography demonstrated a material which has a rate of flow characteristic of 3-oxygen-containing steroids.

4. The possibility that this material might play a part in the etiology of eclampsia is discussed.

5. The placental steroid increases during pregnancy, while the levels of chorionic gonadotrophin remain at a low level.

6. These steroids together with the adrenal steroids may affect the general metabolism of the body and also may sensitize the kidneys so that added factors, perhaps from the placenta, may extend the lesions in these organs so that the function of the kidneys is temporarily altered. Prolonged action of all factors may permanently damage the kidneys.

7. Reversed excretion of placental hormones during the latter months of pregnancy is noted in toxemia, and may reflect failing placental physiology.

8. These studies have significant clinical application and direct our attention to the fact that sodium chloride, particularly, should be restricted as early in the gestation as the one hundred twentieth day.

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Discussion

DR. FRANK E. WHITACRE, Memphis, Tenn.—If a woman in the third trimester of pregnancy dies of accidental causes, in no way associated with toxemia of pregnancy, one finds that striking changes have taken place. Both lobes of the pituitary gland are enlarged to fill the sella turcica tightly. In the posterior lobe there is a marked increase in the number of basophilic cells which are thought to have a relationship to the production of a pressor substance. The thyroid is obviously enlarged, grossly and histologically, and

the basal metabolism rate is known to be increased. Both the medulla and cortex of the adrenals are enlarged and small elevations on the surface have been called physiologic adenomas. It is not an unreasonable assumption that this increase in activity is physiologic as well as anatomic. We, therefore, have no argument with Dr. Hughes that certain of the glands of internal secretion are concerned in the syndrome known as toxemia of pregnancy, but would add that these substances are probably present in all pregnancies.

Many have believed that the placenta produces a pressor substance but it could be argued equally as well that the placenta only gives a stimulus to the production of these substances by the glands of internal secretion. It is common knowledge that in a normal pregnancy and delivery, as soon as the placenta is removed, the glands of internal secretion return to their normal state within five to eight days post partum and toxemia of pregnancy is almost unknown after that time. The question is, then, Why do not all pregnant women have toxemia of pregnancy? It seems reasonable that most of these individuals are sufficiently protected by elimination of these substances by the normally functioning liver. This naturally leads us to consider nutrition and that most individuals receive a proper balance of the first-class proteins, protective vitamins, and minerals. We have reported our findings in a large series of eclamptic patients in China, the Philippines, and the Memphis area, in which almost all the patients were indigent with poor prenatal care and nutrition.

Although we agree that the metabolism of sodium and chloride ions is affected by toxemia, and that toxemia can be aggravated by the administration of salt, we have been unable to demonstrate consistently an excess of sodium in the body during toxemia.

Water is obligatory to salt excretion but the reverse is not true. The antidiuretic principle of the posterior pituitary has been shown to inhibit the excretion of water but not of solutes. It has little effect on the obligatory urine flow, only excess water is held back. This factor seems to render the kidney insensitive to excess water in the blood. This being true, the mechanism of action of hydration therapy must be the dilution of the concentration of antidiuretic principle in the blood stream.

Since the serum sodium levels are not increased during toxemia it is possible to theorize that the factor producing the toxemia more nearly mimics the antidiuretic principle than it does the adrenal steroids. The dilution of this factor by the administration of water decreases the facultative readsorption of water and thereby produces a diuresis and improvement of the patient.

DR. WILLIS BROWN, Little Rock, Ark.—While in certain of Dr. Hughes' tables the data recorded for normal and toxic pregnancies seem to overlap, he has established that in all pregnancies there is an increased concentration of a sodium-retaining steroid which probably is responsible for the edema of pregnancy.

There are certain considerations outside the corticosteroids in toxemia and eclampsia which I think warrant discussion, and I should like to present a point of view and perspective on these changes. Dr. Hughes said that he believed toxemia and eclampsia, although he had only one case of eclampsia, were a "specific clinical entity." There is considerable doubt in my mind that this is true. In the belief that toxemia-eclampsia is a specific clinical entity, we have spent years of study hunting for a specific etiology. These studies of Dr. Hughes' deal with the retention of sodium, and it is suggested that this may be a specific etiology. We also have studied the retention of sodium and water, noting clinical, chemical, and physiological changes, hunting for a specific manifestation. I should like to suggest that these are not specific changes of toxemia but are common in all gravid women. Perhaps the abnormality is only one of degree. It is my interpretation that the basic pathologic physiology of toxemia and eclampsia is probably arteriolar spasm rather than sodium retention.

During the past four years we have had an unusual experience and the opportunity to study 77 convulsive gravid women from among approximately 10,000 pregnancies. Some of these eclamptic pregnancies have been associated with edema and some not; some with obvious sodium retention and some with none; some with obvious renal disease and

some with none; some with cardiac disease and some with none. The clinical picture of the eclamptic syndrome, as we see it in Arkansas, is not a specific disease associated with a specific derangement.

During this interval we undertook to modify and correct the clinical manifestations of the disease—namely, edema, hypertension, and convulsions. Twenty of these patients were managed by effective sodium control. These women were given several diuretics and natro-uretics; mercury, ammonium chloride, hypertonic and hypotonic fluids in varying amounts given intravenously. Their edema was eliminated. Nevertheless, 2 of these 20 women died. There were 17 eclamptic women whose blood pressure was brought below 140 systolic by intravenous *Veratrum viride*. Their hypertension, their arteriolar spasm was effectively controlled. Some of these women continued to have convulsions, despite the fact that their blood pressure was normal or low, and one patient had six convulsions with a systolic pressure below 120. One of these women died. In a third series 40 women were treated by deep sedation with barbiturates and Avertin, and the convulsions were completely controlled. There was a total of only three convulsions among these 40 women after they reached the wards. Three of these women died.

Thus, of the 77 women with convulsive eclampsia in our institution in the last four and a half years, 6 died (Table 1). It seemed to make little difference what the presenting major symptom or the effectiveness of control of each of them might be.

TABLE I. MORTALITY IN ECLAMPSIA*†

	NO. OF PATIENTS	DEATHS	
		NO.	PER CENT
Control of hypertension	15	1	6
Control of convulsions	42	3	7
Control of edema	20	2	10
Total	77	6	5

*From the Department of Obstetrics and Gynecology, University of Arkansas School of Medicine, 1949-1953.

†Effective control of edema, hypertension, and convulsions does not prevent deaths from eclampsia.

We have come to hold the opinion that the physiologic derangements of normal pregnancy set the stage for this disturbance, and that a whole host of situations may precipitate the final clinical syndrome. It may be infection; it may be tissue trauma or placental separation; it may be emotion or fatigue; it may be excessive salt intake, or even excessive water intake. It is suggested that when edema and arteriolar spasm exist in unfavorable combinations, they produce sufficient tissue hypoxia to exceed the tolerance of a given organ, and its compensation is broken with the appearance of appropriate symptoms. This may occur in the kidney, the heart, the liver, the vascular system, or the brain. The breaking point of a given organ is probably determined by any previous injury which that organ has sustained. Thus, the clinical manifestations of this syndrome may include a variety of symptoms, depending on tissue tolerance, the degree of hypoxia, and the precipitating mechanism.

I think it is of some moment, therefore, that we consider that perhaps there is not a single etiology of eclampsia, but that a variety of mechanisms may precipitate this picture. Dr. Hughes has shown us that there is an accumulation of certain salt-retaining substances in toxemia and eclampsia. Undoubtedly, there are many other factors which may cause this syndrome.

Dr. Hughes and his associates have advanced our knowledge of steroid chemistry and sodium metabolism in pregnancy. It appears that all gravid women have these biologic changes in varying degree and that some precipitating mechanism induces generalized or localized hypoxia that sets the stage for decompensation in some vital organ.

DR. NICKOLAS C. LOUROS, Athens, Greece.—The well-known properties of hyaluronidase suggested to us the possibilities of using this enzyme to favor the absorption

of edema fluid. Hyaluronidase accelerates the dispersion and absorption of hematomas as well as of subcutaneous collections of fluid, through the polymerization and hydrolysis of a viscous polysaccharide, hyaluronic acid, which constitutes the primary substance of the intercellular spaces and the adhesive factor of the tissues. It seemed possible, therefore, that hyaluronidase would accelerate the absorption of the fluids resulting from the vagotonic vasodilatation of toxemia to which we ascribe a very great importance.

Our experience showed that after giving three times a day 1 c.c. of Kinetine, which is one of the trade names of hyaluronidase, we had in seven days an enormous loss of weight and an equivalent diuresis. I can give no explanation for this result, but I think it worth while to report on it, because I think it is the first time hyaluronidase has been used for this purpose.

DR. HUGHES (Closing).—I want to thank Drs. Whitacre and Brown for emphasizing some of the points that I apparently did not elucidate. First, there occurs an increased excretion of these adrenal steroids in all pregnancies. Second, we do want to state that this is not the direct cause of pre-eclampsia or eclampsia, but perhaps is a part of the picture. We feel that the mechanism may be set up in all individuals in varying degrees, but that such precipitating factors as disturbance in nutrition, change in the climate, or infection may actually produce the disease. We have also observed patients without edema who still have plenty of fluid retention, particularly in the serous cavities. It is possible that the toxemia which occurs in the South may be different from that found in the North. During the past year we sent our technician to Duke University, where Dr. Carter allowed her to collect urine from toxic patients and analyze these specimens for the material in question. It seemed that the group of patients observed there differed from those in our area. From analysis of the record, they were of the hypertensive vascular or nephritic type.

We have tried the hydration method as recommended by Dr. Whitacre in our clinic. Our results have not been as good as with the dehydration method.

THE IMPORTANCE OF THE FIRM CERVIX IN PROLONGED LABOR*

L. A. CALKINS, M.D., PH.D., KANSAS CITY, KAN.

(From the University of Kansas Medical Center)

IN A recent study of fetal mortality at the University of Kansas Medical Center, it was noted that a considerable number of the otherwise unexplained deaths had occurred in prolonged (more than thirty hours†) labor‡ with a firm§ cervix, at about 7 to 8 cm. dilation. Autopsy on some of these babies showed tentorial tears or subdural hemorrhage, but in most of them only evidence of anoxia was present. The frequency of this type of death made it seem advisable to study again the effect of prolonged labor, and also the effect of the firm cervix on fetal mortality.

In a series of some 7,000 consecutive deliveries, the incidence of the firm cervix was found to be that shown in Table I. The incidence, as here shown, is probably too small, as it is our constant impression that house officers tend to overlook firmness of the cervix if the labor progresses normally. Many times the firmness of the cervix is discovered only when the labor progresses less rapidly than usual, frequency and intensity of the uterine contractions being taken into consideration.

TABLE I. INCIDENCE OF FIRM CERVIX

	NORMAL (OR SOFTER)	SLIGHTLY FIRM	FIRM CERVIX
Nulliparous	1,891 84.0%	215 9.4%	169 7.4%
Parous	4,353 92.5%	257 5.5%	97 2.6%

TABLE II. ETIOLOGY OF FIRM CERVIX IN RELATION TO WEIGHT OF FETUS

	1,500-2,495 GRAMS	2,500-3,995 GRAMS	4,000 GRAMS AND OVER
Nulliparous	20 9.0%	140 7.3%	3 5.4%
Parous	0	81 2.0%	3 1.2%

*Presented at the Sixty-fourth Annual Meeting of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons, Hot Springs, Va., Sept. 10, 11, and 12, 1953.

†We use thirty hours as the dividing line of prolonged labor, as there is little, if any, increase in fetal mortality till thirty hours of first stage labor has been reached.

‡Labor is said to begin in our clinic when the patient experiences the first painful contraction, provided these contractions do not spontaneously (without sedation) cease. We realize that a number of these individuals are not actually in labor for the first several hours or more under such a plan, but have found it the simplest rule we can follow and avoid rather extreme variations in judgment from one house officer to another. We also realize that the incidence of prolonged labor in our clinic is, therefore, higher than in others where such a plan is not followed.

§We estimate the consistency of the cervix at the height of a uterine contraction, and designate as normal that cervix which has the consistency of the lip relaxed, and designate as firm that cervix which has the consistency of the ala of the nose. It is important that this estimate be made at the height of a fairly strong uterine contraction. While it is usually possible to make a satisfactory estimate of cervical consistency by rectal touch examination, examination by vagina is always employed in case of doubt. While relatively few of the normal cervix patients have been examined vaginally, the vast majority of the firm cervix patients have been so examined one or more times.

We still do not know why some cervices are firmer than others. As would be expected (Table II), the incidence in premature labors is somewhat higher, and that in postmature labors somewhat lower than is noted in term pregnancies.

Table III shows the fetal mortality related to firmness of the cervix in nonparous women, without regard to the length of labor. Table IV shows the same data with respect to parous women. It is to be noted that there are few deaths due to trauma when the cervix is of normal consistency. Even a slight degree of firmness of the cervix produces definite mortality of a traumatic nature. The firm cervix is associated with a very high proportion of traumatic deaths.

TABLE III. FETAL MORTALITY—FIRM CERVIX—NULLIPAROUS

NORMAL CERVIX			SLIGHTLY FIRM			FIRM CERVIX		
Anomalies	7		Premature separation	1		Anomaly	2	
Toxemia	5		Brain hemorrhage	1		Toxemia	1	
Premature separation	5		Tentorial tear (48 hours and midforceps)	1		Intrapartum (32, 38, 47, 58, 60 hours)	5	
Syphilis	1		Diabetes	1				
Hyaline membrane	3							
Total mortality	21	1.1%	Total mortality	4	1.9%	Total mortality	8	4.7%
Due to trauma	0	0.0%	Due to trauma	2	1.0%	Due to trauma	5	3.0%
Nontraumatic	21	1.1%	Nontraumatic	2	1.0%	Nontraumatic	3	1.7%

TABLE IV. FETAL MORTALITY—FIRM CERVIX—PAROUS

NORMAL CERVIX			SLIGHTLY FIRM			FIRM CERVIX		
Anomalies	13		Premature separation	2		Anomaly	1	
Toxemia	5		Placenta previa	1		Toxemia	1	
Premature separation	10		Prolapsed cord	1		Premature separation	3	
Erythroblastosis	6		Syphilis	1		Infection	1	
Syphilis	2		Infection	1		Placental insufficiency	1	
Placenta previa	2		Diabetes	1		Accident	1	
Hyaline membrane	17		Hemorrhage	1		Trauma	2	
Prolapsed cord	6		Prolonged labor (30 hours)	1		Prolonged labor (36, 40 hours)	2	
Infection	9							
Miscellaneous	3							
Unknown	14							
Trauma 1,280, 1,465, 1,765, 1,880, 2,885 Gm.	5							
Prolonged labor (38 hours late first stage, firm cervix?)	1							
Total mortality	92	2.1%	Total mortality	9	3.5%	Total mortality	12	12.4%
Due to trauma	6	0.1%	Due to trauma	2	0.8%	Due to trauma	4	4.1%

Table V shows, in outline form, the effect of prolonged labor and firm cervix on fetal mortality. It is to be noted that there are few if any deaths as a result of prolonged labor where the cervix is normal. Moderate increase in consistency raises the mortality to about 7 per cent, and a truly firm cervix produces a high fetal mortality when the labor is prolonged.

TABLE V. PROLONGED LABOR—FIRM CERVIX—TRAUMATIC DEATHS

	NORMAL CERVIX		SLIGHTLY FIRM		FIRM CERVIX	
Nulliparous.—						
Incidence	73	4 %	30	14%	58	34%
Fetal mortality	0	0 %	2	7%	5	9%
Parous.—						
Incidence	29	0.7%	15	6%	18	19%
Fetal mortality	1	3.0%*	1	7%	4	22%

*An unrecognized firm cervix?

TABLE VI. PROLONGED LABOR—COURSE OF LABOR AND THERAPY—NULLIPAROUS PATIENTS

NORMAL CERVIX		SLIGHTLY FIRM		FIRM CERVIX	
Normal course (10.9 hours)	1,746	Softening cervix (17 hours)	108	Softening cervix (19 hours)	59
Fetal mortality	0	Prolonged labor	12	Cesarean section	3
		Fetal mortality	0	Prolonged labor	6
		Improved contractions (12 hours)	51	Fetal mortality	0
		Prolonged labor	1	Improved contractions (16 hours)	46
		Fetal mortality	0	Deep cervical laceration	4
				Cesarean section	3
				Dührssen's incisions	1
				Prolonged labor	5
				Fetal mortality	0
		Always poor contractions (27 hours)	47	Always poor pains (44 hours)	48
		Moderate cervical laceration	2	Moderate cervical laceration	6
		Deep cervical laceration	3	Deep cervical laceration	9
		Cesarean section (22, 24, 27, 52 hours)	4	Very deep laceration	1
		Not prolonged labor (19 hours)	32	Cesarean section	8
		Fetal mortality	0	Dührssen's incisions	3
				Not prolonged labor (18 hours)	7
				Fetal mortality	0
Prolonged labor (40.1 hours)	73	Prolonged labor (43 hours)	15	Prolonged labor (48 hours)	41
Fetal mortality	0	Fetal mortality	2 13%	Fetal mortality	5 12.2%

A more detailed analysis of all of the cases of firm cervix produced the data shown in Table VI and Table VII. It was found that in a large proportion of patients, the cervix tended to soften as labor progressed. While the labor might be prolonged under these circumstances, it was not, on the average, tremendously increased, and no fetal mortality resulted. In a second group of patients, the uterine contractions tended to improve when the cervix was 3 to 5 cm. dilated. In this group, also, there were some instances of prolonged labor, but again no fetal deaths. In the third group of patients, where the cervix remained firm and the patients reached 6 or more cm. dilation without significant improvement in the uterine contractions, the incidence of prolonged labor was very high (41 out of 48 nonparous and 11 out of 34 parous

patients). Here, there was a marked increase in moderate to severe trauma to the mother, and a very high fetal mortality—12 per cent in primiparas and 36 per cent in multiparas. It appears, then, from the study of this small series of 7,000 patients, that it is the combination of (1) firm cervix, (2) prolonged labor, and (3) consistently poor uterine contractions (beyond 6 cm. dilation) that is so dangerous to the baby and damaging to the mother. No two of these three factors produced fetal death in this series, but the combination of all three proved very damaging.

TABLE VII. PROLONGED LABOR—COURSE OF LABOR AND THERAPY—PAROUS PATIENTS

NORMAL CERVIX		SLIGHTLY FIRM			FIRM CERVIX		
Normal course (7 hours)	4,353	Softening cervix (11 hours)	104		Softening cervix (12 hours)	27	
Fetal mortality	0	Deep cervical laceration	1		Moderate cervical laceration	2	
		Prolonged labor	15		Prolonged labor	1	
		Cesarean section	1		Fetal mortality	0	
		Fetal mortality	0		Improved contractions (14 hours)	32	
		Improved contractions (9.7 hours)	97		Deep cervical laceration	1	
		Moderate cervical laceration	1		Prolonged labor	3	
		Prolonged labor	1		Fetal mortality	0	
		Fetal mortality	0				
		Poor pains (19 hours)	52		Poor pains (25 hours)	34	
		Deep cervical laceration	1		Moderate cervical laceration	1	
		Not prolonged labor	43		Deep cervical laceration	1	
		Fetal mortality (1,020 grams)	1	2.3%	Not prolonged labor	23	
					Cesarean section	3	
					Fetal mortality	0	
Prolonged labor	29	Prolonged labor	9		Prolonged labor	11	
Fetal mortality	0	Fetal mortality	1	11%	Fetal mortality	4	36%

Procedure

The plan of procedure in our clinic, as a result of this study, is as follows: Everyone is admonished to judge carefully the consistency of the cervix as early in labor as possible. If the cervix be normal, no particular effort is made to avoid prolonged labor, for even if it be prolonged, food, fluids, and sedation will take care of the problem. If, however, the cervix is found to be firm, consultation is to be called at the end of not more than sixteen hours, with the idea that sufficient opportunity shall be provided for the initiation of proper therapy in an effort to complete the first stage before a total of thirty hours has passed.

Since we have no control over the desired softening of the cervix, other than the use of sedatives, they are to be employed, particularly if not previously exhibited. We have not yet found a better antispasmodic than the combination of morphine and atropine. Demerol has been used but little, and, in my opinion, with less favorable results than are obtained from morphine.

We have, so far, confined our efforts at improving uterine contractions to the use of the upright position, the abdominal binder, and artificial rupture of the membranes. This latter procedure seemingly helps in some instances, but analysis of a large series of cases would indicate that it is regularly effective only if performed very early in labor.

We now feel quite secure in the use of intravenous Pitocin in the presence of a normal cervix, but have, as yet, had too little experience with its employment in the presence of a firm cervix to offer any recommendations. It seems, from the data previously presented in connection with the normal occurrence of increased uterine contractions, that it might be advisable to bring them about in a carefully restricted manner. Paravertebral block anesthesia has, in our hands, been very effective in increasing the intensity of uterine contractions; and, in some instances, has seemed to bring about softening of the cervix. Our experience is still too limited to permit conclusions. We have employed Dührssen's incisions infrequently, but believe they have a place when dealing with a low station and a dilation of not less than 7 or 8 cm. It is our definite impression that, following Dührssen's incisions, the immediate application of forceps is not advisable.

In properly selected cases, cesarean section can be safely utilized. This is not to say that cesarean section should be the routine treatment in these patients, but rather that its employment in something less than one-third of 1 per cent of our patients fulfilling the criteria of prolonged labor, or almost prolonged labor, with persistently firm cervix, and still very poor uterine contractions, will reduce our fetal mortality from trauma almost to the vanishing point.* It should probably be employed at a time not too far removed from thirty hours of first stage labor. In one patient in this series, a cesarean section done at the end of 57 hours with no obvious fetal distress resulted in a baby with a tentorial tear who died two days later. In the 22 cesarean sections so far done for this indication, 4 patients have been morbid on the basis of the American Committee standards.

Conclusion

The combination of the relatively minor clinical conditions of prolonged labor, persistently firm cervix, and continuing poor uterine contractions, is another example of the merging of several relatively minor difficulties to form a major complication, inimical to the best results for the mother, and positively dangerous to the welfare of the baby.

Discussion

DR. WILLIAM J. DIECKMANN, Chicago, Ill.—A firm cervix is usually the cause of prolonged labor. Both conditions are easy to discuss but very difficult to define and to treat. Some of us learned our obstetrics by vaginal examinations and we know about cervical effacement, dilatation, and consistency as depicted in Bumm.

*The contracted pelvis is quite carefully screened in our Dystocia Clinic, and is treated by elective cesarean section or section after a moderate trial of labor. Only one patient in this series, with a moderate midpelvic contraction, who also had a firm cervix and prolonged labor, could be said to have lost her baby because of pelvic contraction.

For many years I have been making periodic sterile vaginal examinations from the thirtieth week of pregnancy up to delivery. I have tried, on several occasions, to obtain x-ray evidence of the changes without much success. On vaginal examination, one can determine approximately the following three periods for primigravidas and multiparas: 6 to 4 weeks, 4 to 2 weeks, and 14 to 0 days before delivery. Labor before the cervix was "ripe" is the cause of some of our cases of prolonged labor due to cervical dystocia which Calkins describes as the firm cervix. Several years ago we made a careful study over a period of two months, of all patients admitted to the birth rooms. There were 765 of whom 102, 13 per cent, were diagnosed being in "false labor," in that the patients were discharged or sent off the birth-room floor and were comfortable for 24 or more hours. Some of these patients did not deliver for as long as three weeks. Obviously, had any of these patients been stimulated by stripping or rupturing the membranes and/or by an oxytocic injection, labor would have been prolonged because of the firm cervix.

We define prolonged labor as a duration of over 24 hours. However, several recent studies in our hospital have shown that the mean duration of labor in the primigravida is approximately 12.5 hours, and in the multipara is 7.6 hours. I believe 24 hours is too long. We do not expect every patient to deliver in that period of time. The number of contractions per hour, the duration, and the intensity of the contraction are all very important factors. We all agree that hard, usually painful contractions every 3 minutes, lasting 40 to 50 seconds, will result in cervical dilatation or laceration and descent of the presenting part, or uterine rupture.

I note that Calkins accepts Dührssen's incisions as an occasionally necessary operation. We believe that this operation, with 5 to 6 cm. dilatation and the head at or above the spines, is an admission of error in judgment. The patient should have been delivered earlier by cesarean section. We have, during the last three years, performed a number of low cervical sections in patients who have been in labor and/or had ruptured membranes over 24 hours without any difficulty. However, the patients are carefully selected, extra care is taken to prevent spill, a peritonitis routine is maintained for 72 hours or longer, depending on the symptoms and signs, and antibiotics may be injected. *I am still definitely opposed to cesarean section after failed forceps, or version after failed forceps.* These are the cases that should have had an early cesarean section if the doctor were familiar with the various aspects of dystocia. If a rim of cervix (meaning 8 or 9 cm. dilatation) persists for one, and at the most, two hours with the head engaged, it is best for the mother, and especially for the baby, to perform Dührssen's incisions, episiotomy, and a low forceps delivery.

There is no question but that a firm cervix causes an increased morbidity and mortality for the mother.

What happens to the baby? I have read four recent reports on the results to the baby after prolonged labor or difficult forceps deliveries. The babies have been studied from 2 to 31 years after delivery. Precipitate delivery (less than 2 hours), prolonged labor, (a firm cervix), and difficult mid- or high forceps delivery are certainly associated with an increased stillbirth and neonatal death rate. It is of interest that, in all four reports where the babies were studied years later, those who survived the difficult forceps deliveries had a lower incidence of eye defects and a higher intelligence rating than those born after a precipitate delivery.

In Table I are shown representative percentages for our service over a twenty-one year period. There is a marked decrease in the incidence of prolonged labor and in the total stillbirth and neonatal death rates (1,000 grams or more). The incidence for Dührssen's incisions remains about the same. There is a slight increase in the cesarean section rate. We believe this indicates that we are diagnosing and treating labor more accurately and are not stimulating patients who are not in labor or who are in false labor.

In Table I are also shown the figures for mid- or high forceps and the stillbirth and neonatal rates and birth injury figures for these deliveries. Again there is a decrease in these difficult forceps deliveries and a decrease in the stillbirth and neonatal rates and a marked decrease in the number of birth injuries.

In Table II are shown the data for two three-year periods of patients who had prolonged labor compared with the total deliveries for the same periods in the hospital. There is a marked increase in the use of cesarean section in patients with prolonged labor although the number of cases is small. The percentages of Dührssen's incisions has also increased. The stillbirth and neonatal mortality is still higher than for the hospital as a whole but it is not too much out of proportion in these complicated cases. The diagnosis of a firm cervix must be established within the first 24 hours of labor and a plan of treatment decided for each patient.

TABLE I. OPERATIVE DELIVERIES AND STILLBIRTH AND NEONATAL MORTALITY FOR VARIOUS YEARS (PER CENT)

	1932	1939	1947	1951 AND 1952
Stillbirth	2.32	2.15	0.86	1.08
Neonatal	?	2.21	1.15	0.87
Cesarean section	4.7	5.3	5.4	5.2
Dührssen's incisions	1.1	2.1	0.9	0.7
Prolonged labor	13.9	8.7	3.8	2.3
Mid- or high forceps	3.8	3.3	2.3	1.4
Stillbirths	4.6	3.0	2.3	–
Neonatal	2.8	5.0	0	–
Birth injury (No.)	1	1		
	1931-1940	1941-1945	1946-1950	1951-1952
Birth injury—%	0.53	0.12	0.09	0.05

TABLE II. PROLONGED LABOR AND FIRM CERVIX (PER CENT)

	1936-1939		1946-1949	
	PROLONGED LABOR	TOTAL DELIVERIES	PROLONGED LABOR	TOTAL DELIVERIES
Deliveries (No.)	384	7,970	100	12,203
Spontaneous	24.0	59.0	3.0	23.0
Forceps, low	40.0	27.0	41.0	68.0
Mid- or high	24.0	4.0	27.0	1.6
Version and extraction	2.3	1.0	0	0.7
Cesarean section	6.7	5.5	22.0	5.0
Craniotomy	0	0	2.0	0.01
Breech extraction	2.6	4.0	5.0	1.5
Dührssen's incisions	16.0	1.0	26.0	1.0
Maternal mortality	0	(10) 0.13	0	(4) 0.04
Total fetal mortality	?	3.7	4.0	1.9

Much has been written about the caloric requirements of the woman in labor, the acidosis which requires treatment, and the need for rest. For the labor of 24 to 36 hours one need only supply sufficient fluids to insure at least 1,500 ml. of urine per 24 hours. The ketosis in the normal individual requires no treatment; actually, I believe it is protective for the urinary tract. The CO_2 and pH in the cases studied have never dropped to dangerous limits and they will not, except in the diabetic or the severely nephritic patient. A certain amount of rest is necessary; it is immaterial whether one uses morphine or chloral hydrate and bromides by rectum. The important part of the treatment is to recognize as early as possible those patients in whom labor is not progressing normally, which can be done by observing the patient for a half hour at frequent intervals and by periodic vaginal examinations to determine the condition of the cervix and descent of the presenting part.

Maternal deaths still occur but as the percentage of deaths due to toxemia, hemorrhage, and sepsis has decreased, deaths due to the less frequent causes such as prolonged labor have risen proportionately.

The stillbirth and neonatal death rates have also decreased but can be lowered still more. Prolonged labor still results in maternal death from (1) difficult vaginal delivery by

relatively untrained doctors (causing hemorrhage and shock) and (2) cesarean section with death from hemorrhage and shock, embolism, or sepsis.

As teachers we can lower maternal, stillbirth, and neonatal rates and decrease fetal injuries by advocating repeated sterile vaginal examinations and training the residents in the proper use of forceps, Dührssen's incisions, and cesarean sections.

DR. L. M. RANDALL, Rochester, Minn.—The terms uterine inertia and cervical dystocia are commonly mentioned in the literature. Where one begins and the other leaves off is difficult to know for they, as a rule, are but part of the whole picture—abnormal uterine synchronization. Aberration in behavior of the whole uterus probably has much to do with the mechanical complications of labor, largely because it is often not recognized early and therefore inadequately managed. Pelvic mensuration, recognition of true cephalopelvic disproportion, accurate diagnoses of position and presentation, and the observation of the mechanisms of labor are in general well accomplished. However, too frequently we find cephalopelvic disproportion mentioned in histories as the indication for cesarean section, when the basic reason was faulty uterine dynamics. Therefore, any useful physical sign that will aid in such a diagnosis should be carefully considered.

One may not discuss this subject without mentioning Reynolds who has taught us some basic facts concerning characteristics of normal and abnormal uterine contraction as recorded on a tokodynamometer.

In the everyday practice of obstetrics, however, we must apply this knowledge, not with precision instruments, but with what our senses tell us. Here, then, enter the differences in training, experience, and ability to use our senses. The observable difference between a good uterine contraction and a poor one is not always exact, nor is the accomplishment of these two types of contraction always the same. The interpretation among us of the consistency of the uterine cervix during labor would also vary appreciably. Many of us might not wish to accept thirty hours as the division between normal and prolonged labor. Would we all agree as to the degree of dilatation of the cervix necessary before rupturing the membranes artificially? These considerations are not important in my opinion. Those that are important are the early recognition of uterine misbehavior and the management thereof, as the author properly emphasizes.

I agree that morphine and atropine are most effective medications for these patients but find that adequate doses of other sedatives such as Demerol are also effective. Rupture of the membranes is good treatment and should be performed even late in the course of labor before deciding on operative delivery. I am reluctant to rupture membranes too early in the course of these labors—some of these patients are not actually in labor. The abdominal binder is a useful and presently rather neglected method of treatment. Perhaps the present-day patient in labor spends too much time in bed, thereby diminishing the normal vis a tergo.

Dührssen's incisions properly employed will always have a place in the treatment of end results of abnormal uterine dynamics. Make the posterior incision first as it may be all that is necessary. If not, do both of the other incisions. Then let the patient have several contractions to allow some retraction of the incised cervix before applying forceps; spontaneous delivery may occur. Dr. Calkins mentions cesarean section rather too apologetically by "this is not to say that cesarean section should be routine treatment for these patients." Naturally that is true. However, careful observation and evaluation of each case will result in a justifiable cesarean section for a definite percentage of these patients.

We have been discussing a facet of the abnormal physiology of pregnancy. One of our great deficiencies in obstetrics is the void in our knowledge of the physiology of pregnancy.

DR. MILTON POTTER, Buffalo, N. Y.—Not once during the discussion of this paper has any mention been made of the importance of the emotional habits of the patient as

a contributory cause of the firm cervix in prolonged labor. It appears to me that we must pay more attention to the education of our patients during the prenatal period. It has been my experience over the past several years that taking time personally to educate patients and their husbands about the problems of pregnancy is worth while. It has been a great surprise to me that much of their anxiety, fear, and doubt has been allayed by our informal group get-togethers, so much so that I am having difficulty today in catching them at the end of the first stage of labor. I am now becoming quite an expert in low forceps. This procedure alone has markedly reduced the duration of the first and second stages of labor.

DR. CALKINS (Closing).—For years it has been my practice to meet the patient as she walks onto the hospital floor. While one cannot definitely tell when examination is made at that time whether the cervix is firm, I like to give the patient morphine if there is any doubt and stop the contractions she is having. Certainly I would agree that a patient with a firm cervix is a very poor candidate for any method of stimulation of uterine contractions at that time.

I agree with Dr. Potter completely. Dr. Starr pointed out to this group a few years ago that prolonged labor was three times as common in their clinic patients as it was in their private patients. That was obviously the result of education of the patient, such as Dr. Potter is now recommending. It has also been my experience that residents throughout the years have queried me as to why so few of my own patients have prolonged labors.

PREGNANCY FOLLOWING MALIGNANCY*

WILLIAM BENBOW THOMPSON, M.D., LOS ANGELES, CALIF.

THE days of our lives tend to fall into a rather well-defined pattern. We are born, we struggle through adolescence and become adults, we marry and have our families, and gradually sink into senility unless rescued from that dismal condition by one of the diseases or disorders to which we are subject. The development of cancer is but one of the events that may disturb this more or less orderly sequence, but even cancer may be said to observe a pattern. Usually it manifests itself in the latter half of life. In women, it therefore usually occurs after the more fruitful years of reproductive activity. Thus, the biological needs for the perpetuation of the species ordinarily have already been accomplished before the "cancer age" has been attained.

It is obvious, then, that the occurrence of a pregnancy after a woman has had a cancer is not often encountered. Primarily, this is due to the age of the patient when the cancer is first detected. A secondary factor is that the treatment of cancer, to be effective, is necessarily destructive. As part and parcel of the therapy, sterilization of the patient is quite common. This may either be due to the surgical procedures employed, or result from radiation. The two factors —age plus treatment—make pregnancy after operations for malignancy a rare condition. Most of my confreres whom I have questioned have not recalled a single such patient, while a smaller number have each had a single case, and have given me detailed records. In my own practice, Fate has been more generous. Five, and possibly six, of my patients represent these abnormal sequences, and this is merely a report of my experience.

Sarcoma of Bone

Sarcomas are less prone to be restricted to an age grouping than are carcinomas in general. Possibly sarcomas arise more often after definite trauma, and hence might logically be seen more often in active younger people than in their more sedate elders; but possibly this ascribing of malignant change to a single blow may merely be *post hoc* reasoning. Whatever the etiology, treatment means loss of the affected tissues. When malignancy affects one of the long bones, the result is mutilating and often tragic. On the credit side, however, is the fact that if the entire tumor is removed before metastases have implanted, secondary growths are rare. When they survive the initial surgery, these people can then adjust their lives without the feeling that they walk constantly in the valley of the shadow. Ovarian function and reproductive faculties are unimpaired, and their subsequent obstetrical experiences present no particular problems. Two of my patients are in this category.

*Presented at the Sixty-fourth Annual Meeting of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons, Hot Springs, Va., Sept. 10, 11, and 12, 1953.

One of these I first saw on Oct. 25, 1948, when she was 24 years old. She had lost her entire left arm at the age of 11, when it was removed by Dr. William Beebe of Ann Arbor, Mich. After considerable effort, the pathologist's report was obtained and is as follows:

> "The specimen consists of an arm amputated at the shoulder joint. The lower 13 cm. of the humerus contains a fusiform tumor growth terminating just proximal to the articular surface and enveloping slightly more than three-fourths of the circumference. The tumor in its central area is soft and hemorrhagic. Sections of the tumor show small spindle cell sarcoma containing nests of round cells and actively infiltrating the adjacent tissues."

Unfortunately, the tumor tissue was lost some time later in the bursting of a steam pipe in the pathological laboratory. Slides were not filed with the Bone Sarcoma Registry, and so the report as given is all that may be shown. This patient delivered a girl baby on June 13, 1949, and a boy on Feb. 19, 1952, and now considers her family complete.

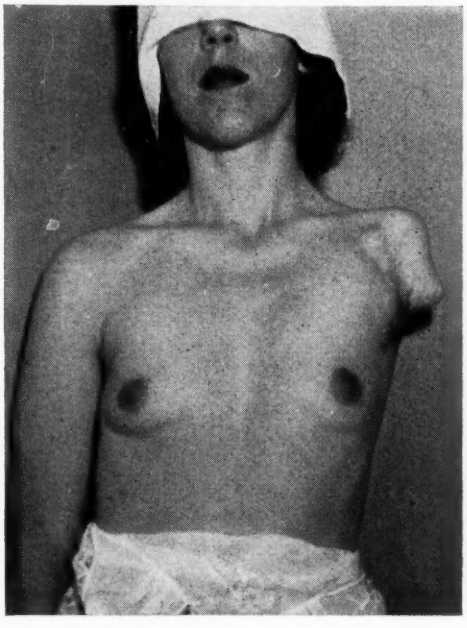

Fig. 1 (Mrs. M. S.).—Sarcoma of humerus removed at age 11.

My second postsarcoma patient came to me on Jan. 5, 1950. Her right leg had been disarticulated at the hip when she was only 4½ years old because of osteogenic sarcoma of the femur. I have written the hospital where this was done, but thus far have been unable to secure any further details. She married at 27, and a little over a year later was delivered in an Army hospital at Frankfurt, Germany. The infant lived only thirty-six hours. According to her account, the infant's cranial bones "had all calcified at six months." It seems reasonable to assume that an impossible amount of molding was required to force the head through her much distorted pelvis. Her second pregnancy was terminated by cesarean section on June 8, 1950.

Carcinomas present more complex problems than do the connective-tissue growths. The generative tract is more often concerned, both in the surgical approach and in the postsurgical radiation. Approximately half of the cancers in women, however, are found in breasts, and roughly one in eight to ten in

ovaries and elsewhere outside the uterine corpus and cervix. Age permitting, treatment of these tumors may not destroy the essential femaleness of these patients, as is evidenced by this report.

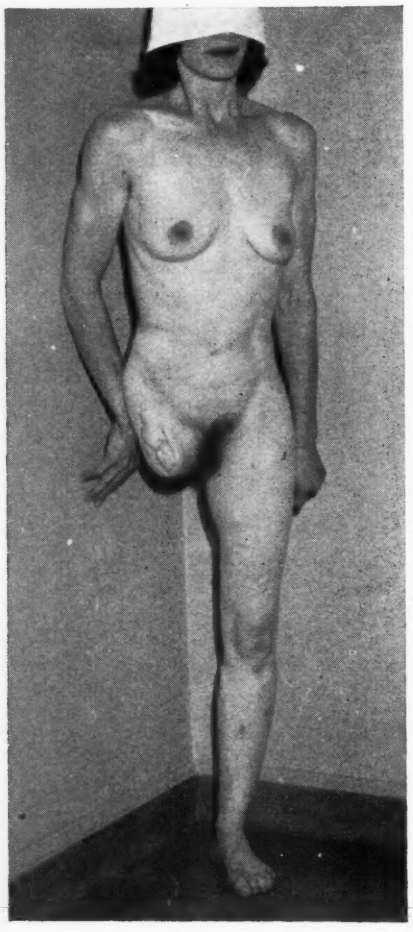

Fig. 2.—Sarcoma of femur removed at age 4½.

Carcinoma of the Breast

Breast tumors have long been viewed with grave suspicion. Even the laity recognize the importance of early study and diagnosis, but sometimes this educational emphasis misfires. My patient with suspected malignancy of the breast may have suffered from self-diagnosis.

Mrs. A. M., having been married seven years with one possible miscarriage in 1941, first came to me on June 7, 1946, as a sterility problem. She was 40 when she decided to seek some solution to her childlessness. In her history, she stated that in 1942 she had noted a lump in the left breast, and had consulted a nurse relative who suggested that she go to a "cancer hospital" in the Midwest for diagnosis and care. At this hospital, the tumor was pronounced cancer. No biopsy or surgery was done. Instead, the entire breast was eroded off with an escharotic paste, the pectoral muscles being preserved. It probably was fortunate that no attempt was made to destroy the axillary nodes. She was, and is, entirely at ease

mentally since she has a written guarantee that the cancer will not recur. Incidentally, in 1949, a small nodule did develop on the edge of the scar, and was removed by a surgical colleague. This was not malignant.

This patient seemed almost beyond help so far as her complaint was concerned. To my surprise, however, she eventually carried a pregnancy to term after a couple of early abortions and was delivered by cesarean section on Aug. 12, 1948. Lactation from the remaining breast was not attempted.

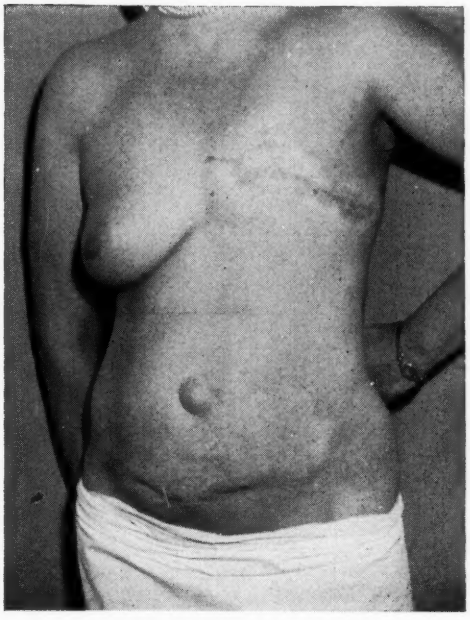

Fig. 3.—Breast removed with escharotic paste.

Not all breast tumors are so readily disposed of. Through the courtesy of Dr. George E. Judd is presented the following:

Mrs. K. B., aged 34, had an uneventful pregnancy and delivery on Feb. 4, 1952. For two or three weeks she attempted to nurse her infant, but this proved insufficient and inconvenient. At her six weeks post partum examination, no abnormalities of the breasts were noted. Six weeks later, however, there was a different picture. She had noted a bloody secretion from the right nipple, and this breast contained a mass about 7 by 5 cm. in the outer upper quadrant. It was not clearly circumscribed. Five days later, on May 10, 1952, a radical mastectomy was done.

> "There is present duct carcinoma in situ manifested by the presence of large rounded spaces completely filled by tumor cells which are polygonal in outline and have vesicular nuclei, with hyperchromatic nuclei in which there are enlarged nucleoli, but not mitotic figures. . . . In other places similar tumor tissue is definitely infiltrating, having left the pre-existing duct wall and invading stroma. There are other areas in which the carcinoma appears to arise within the lobules themselves.
>
> "Ductal carcinoma (infiltration in situ) of breast. Grade I."

Less than a year after surgery, on April 23, 1952, this girl was again delivered by Dr. Judd. She was seen on June 9, 1953, and no recurrence has appeared thus far.

Carcinoma of the Ovary

Studies of ovarian malignancies have shown but little improvement in the percentage of five-year cures in the past twenty years.[1, 2, 3] These tumors arise in hidden recesses, and often are extensive when first detected. Many are resistant to radiation, although that should not be assumed from the pathological picture. Since metastasis to the second ovary is frequent, even an innocent-appearing ovary is seldom allowed to remain if the sister is cancerous. When this is permitted, and the remaining ovary does not later become involved, one of my pathologist acquaintances has suggested that the original tissue be restudied to see why the diagnosis was in error. This was said facetiously, but nonetheless contains more than a grain of truth.

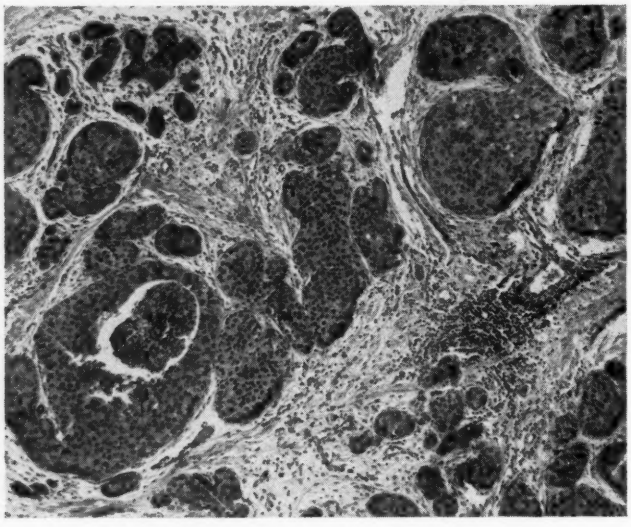

Fig. 4.—Ductal carcinoma of breast.

Pregnancies after ovarian malignancies, then, are highly infrequent, and hence of more than casual interest. Benson, Sherman, and Lucia[4] have recently reviewed the papillary cystadenocarcinomas seen at the University of California Hospital in the twenty-year period from 1932 to 1952. Two of their 137 patients became pregnant "several times" after the removal of one ovary. Incidentally, 16 of the 128 patients "at risk" for three or more years were under 40 years of age when the diagnosis of ovarian malignancy was made. One may assume that the 2 patients who later became pregnant were in this younger group. While the mathematical formula appears simple—one-eighth are under 40, and one-eighth of these will conceive—I cannot believe that pregnancies will follow in so high a proportion. I have seen one case.

Mrs. M. C., aged 20, came to me on April 18, 1951. Her last menstrual period was on Jan. 14, 1951. After establishment of the menarche at 12, she had a normal menstrual history until a secondary amenorrhea developed at the age of 15. She consulted Dr. Arthur F. Buckley of New Bedford, Mass., who found "a large movable mass on the left side extending from the pelvis superiorly 3 cm. above the umbilicus occupying almost the entire abdomen

in this area, and extending 3 or 4 cm. to the right of the midline.'' On July 31, 1946, Dr. Buckley and his associate, Dr. James S. Manley, removed this mass, which proved to be a left ovarian cyst measuring 15 to 20 cm. in diameter. ''There was a moderate amount of pseudomucinous material in the pelvis, largely pooled in the cul-de-sac. There were many small, yellow, fatty-like implants in the cul-de-sac, on the posterior wall and on the sigmoid.''

The pathological report notes:

> ''. . . columnar epithelium with heaping-up with pseudo-glandular arrangement occasionally and some fusing of tips. The cells here appear rather more irregular with several nuclei and occasional cells, and with occasional mitoses, although not very many are seen. . . . Occasionally, the epithelial nests or pseudo glands or cysts of the tumor extend fairly close to the serosa. No definite tumor, however, is found outside.
>
> ''Cystadenocarcinoma of ovary, low grade malignancy (no extension through wall).''

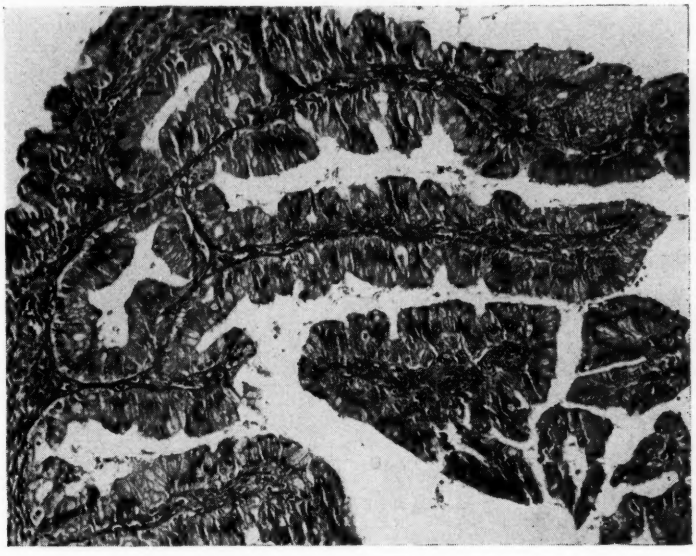

Fig. 5.—Papillary cystadenocarcinoma of ovary.

Because of her youth, and relying upon the pathologist's report, the right ovary was left intact. Three years later, the girl married and promptly became pregnant. This was terminated in New York by therapeutic abortion. A second pregnancy soon followed, and she was delivered by Dr. Buckley on Sept. 10, 1950. I attended her third pregnancy and second delivery Oct. 10, 1951, barely beyond the fifth anniversary of her operation.

As has been noted, the dividing line between papillary cystadenocarcinoma and papillary cystadenoma is not sharply defined. There are some shades of gray between black and white, and not always is one justified in his original estimate. Dr. Leon Krohn has kindly consented to my including the record of a confusing picture.

Mrs. B. F., aged 24, was seen in January, 1946. She had been told two years earlier that there was a right adnexal mass. On Jan. 28, 1946, Dr. Krohn removed the right ovary, ''which contained a cyst of the ovary which was about 7 cm. in diameter and the surface of which was covered with several irregular cauliflower-like growths. The left ovary was slightly enlarged and cystic and contained several smaller but similar papillary growths.'' The

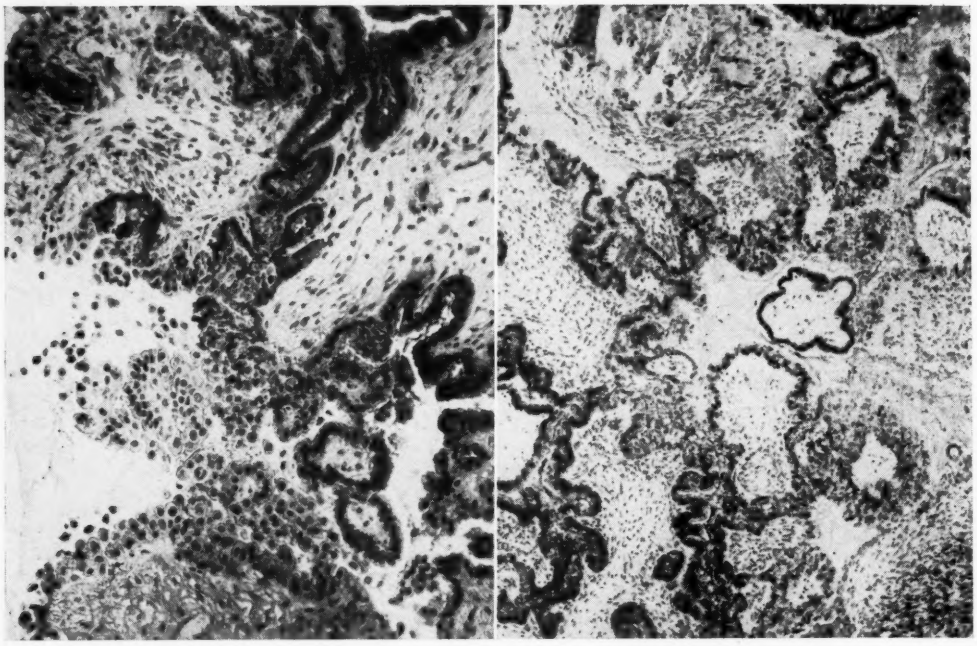

Fig. 6. Fig. 7.

Figs. 6 and 7.—Papillary cystadenocarcinomas (?) of right (Fig. 6) and left (Fig. 7) ovaries.

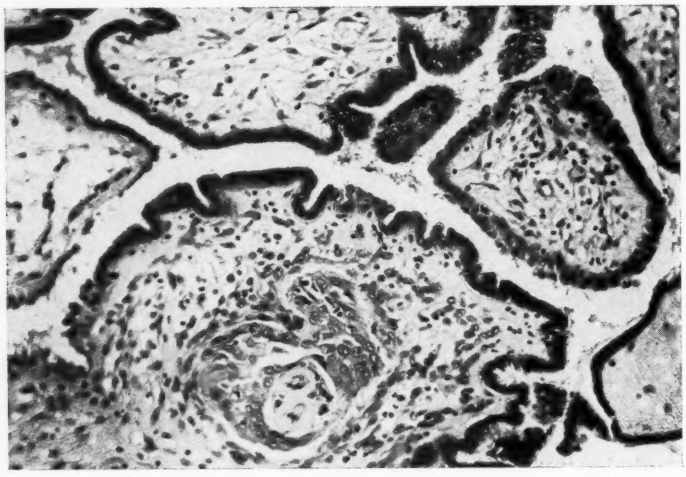

Fig. 8.—Papillary cystadenoma (?) of ovary.

affected portion of the left ovary was also removed, leaving the normal-appearing portion. Frozen sections were prepared, and the immediate judgment was that the tumor was nonmalignant. When the later sections were studied, the pathologist decided that he had erred, and reported bilateral papillary cystadenocarcinoma of the ovary. After much mental turmoil and consultation, it was decided not to reoperate upon this patient but to watch her closely. No radiation was employed. Two years later, Jan. 30, 1948, she was delivered of a living child. On May 22, 1952, following a minimal menstrual disturbance, Dr. Krohn did a total hysterectomy. The resected left ovary was then studied, together with the original tissue from that side, and a second pathologist felt that the original diagnosis of benign growth should have been maintained.

Carcinoma of the Bowel

Malignancies of the rectum and sigmoid colon are anatomically located so close to the pelvic organs that their removal without destroying childbearing function would seem almost impossible.

That it could happen was brought to my attention when I was consulted by Mrs. E. K. on Jan. 19, 1951. She was 39, and had two children, then aged 10 and 12. On Oct. 18, 1949, Dr. William H. Daniel had removed the anus, rectum, and sigmoid for a total length of 26 cm. because of carcinoma involving the anterior wall of the rectum about 5 cm. within the anus. In the dissection, the posterior wall of the vagina was removed for an area of about 4 by 6 cm. At operation, there was no evidence of regional or distant nodules and the liver seemed normal to palpation.

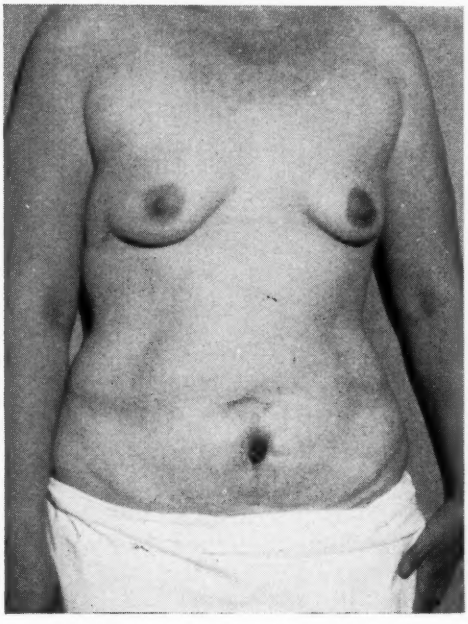

Fig. 9.—Permanent colostomy.

"The tumor is composed of tall columnar mucus secreting epithelial cells irregularly arranged into glands and exhibiting marked hyperchromatism of their nuclei, prominent nucleoli and rather numerous mitotic figures. The tumor extends two-thirds of the way through the musculature of the bowel but does not invade the serosa. A section was made through and through between the tumor and the attached vaginal wall. This section shows no tumor in the vaginal wall but a good deal of inflammatory reaction between the vagina and rectum in the septum. Sections of lymph nodes show no metastases.

"Adenocarcinoma of rectum, Grade II."

Some thirteen months after surgery, Mrs. K. found she was pregnant. The Friedman reaction was positive. I could make out little from pelvic examination except a peculiar sacculation of the posterior vaginal wall, which was apparently covered by smooth vaginal mucosa, and a soft and discolored cervix. The whole lower abdomen seemed a solid mass, and the corpus uteri could not be outlined. Some 5 cm. below the umbilicus was the colostomy opening. Therapeutic interruption of pregnancy was authorized by the Abortion Committee

of the Hollywood Presbyterian Hospital and was carried out by me on Jan. 29, 1951. The same chain of events, with the same findings, was terminated again on Nov. 3, 1951. Following that episode, Mr. K. had a vasectomy performed.

Dr. Daniel then recalled a previous similar patient of his from twenty years ago. Mrs. M. B., aged 25, was delivered on Aug. 6, 1933, of a 4¼ pound infant some seven weeks prior to her expected date. She had had "colitis" for two years, with blood in the stools frequently, but this never had been investigated. At delivery, even the intern noted her pale, waxy color. Eight days later, the hemoglobin was reported as 20 per cent, with only 1,800,000 red blood cells. Transfusion of 500 c.c. of whole blood was given the next day. She left the hospital on the twenty-first day, with the hemoglobin up to 37 per cent. Three months later she was referred to Dr. Daniel because she had not gained strength after delivery and still was troubled with colitis. A biopsy showed a highly malignant adenocarcinoma.

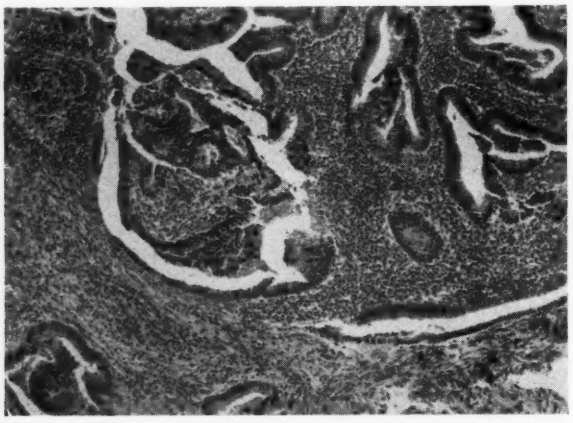

Fig. 10.—Adenocarcinoma of rectum.

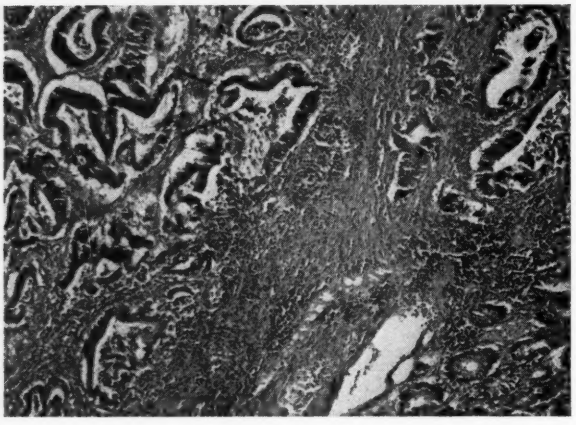

Fig. 11.—Adenocarcinoma of rectum.

On Dec. 6, 1933, the same procedure was done that has been described for Mrs. K., except that the rectovaginal septum was not removed. The colostomy opening was in the left lower quadrant. In reperitonization of the pelvis, the fimbriated ends of the tubes were buried under the newly located peritoneum. Transfusions were not lightly considered in 1933, but she was given 500 c.c. of blood on the operating table, and 300 c.c. more on the next day. While her immediate condition was anything but good, she recovered sufficiently to be discharged on the fourteenth day.

"Microsection shows typical adenocarcinoma with fungating tendencies, marked secretory activity and considerable inflammatory reaction. It is invading the musculature extensively. There is marked eosinophilia. Quite a little epithelial proliferation. The irregular size of cells and nuclei, pyknotic staining, would suggest that this might be a type IV adenocarcinoma."

Despite the attempt at tubal sterilization, this patient again became pregnant and was delivered vaginally in August, 1936. Dr. Henry Gernand, who attended her, tells me that while his records became hopelessly jumbled during his service in the Navy, he can recall vividly much detail of the delivery. For one thing, he decided to avoid cesarean section if possible, since the colostomy opening was closely adjacent to any operative field, and the pelvic anatomy was undoubtedly much distorted. For another, this was the only time that he could not determine the progress of labor by rectal examination. He did a midline episiotomy without fear of third-degree involvement, and carried this incision almost to the tip of the coccyx. His worries and patience were rewarded by the safe delivery of a boy just under 7 pounds. Mrs. B. moved from the area, and the last known state of her health was obtained when she sent Dr. Gernand a picture of her son when he was 5 years old, at which time she wrote that all was well with her.

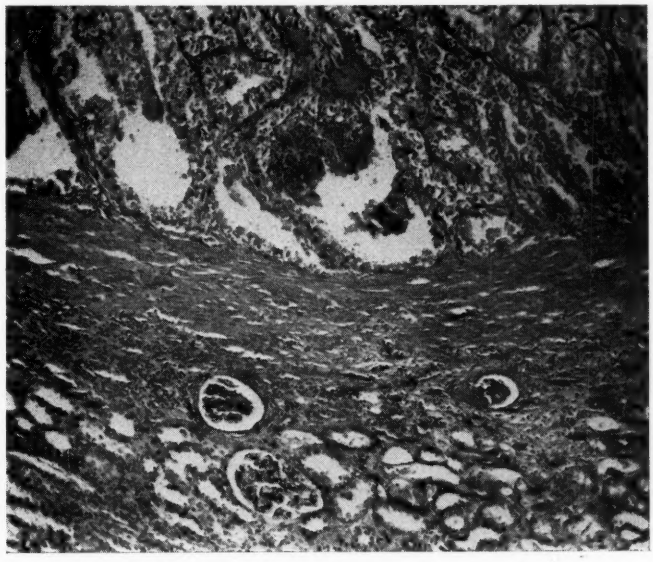

Fig. 12.—Adenocarcinoma of the kidney.

Carcinoma of the Kidney

Cancer appearing in tissues distant from the pelvic organs and adjacent structures influences the conduct and outcome of future pregnancies in two particulars. Chief of these is the time interval between the treatment of the cancer and the establishment of pregnancy. The other is a consideration of how a later pregnancy may have been affected by secondary radiation. The longer the time "at risk" with no recurrence, the less hazardous is the additional physical and physiological strain of carrying a pregnancy. As to the possible dangers arising from increased radiation of primordial ova, our data are most incomplete, and quite probably will so remain.

Mrs. M. K., aged 37, was first seen on March 19, 1951, then seven weeks beyond her last period. On April 26, 1945, she had had a right nephrectomy done for adenocarcinoma.

> "Section is composed predominantly of irregular glandular structures lined by papillary tall columnar epithelial cells with clear cytoplasm and nuclei often aplastic. The lumens are filled with colloid. Mitosis occurs infrequently alternating with fibrosis. There are numerous vessles and areas of hyalin degeneration, hemorrhage and small calcium deposits. A narrow capsule of collagenous fibrous tissue separates the tumor tissue from the parenchyma of the kidney, which reveals regular tubules. Glomeruli show areas of round cell infiltration in the interstitial tissue."

Within a month after the surgical approach, deep x-ray therapy was begun and carried out over the next four months. A total of 6,000 R.U. was given, aimed from anterior, posterior, and lateral angles, and with the pelvis screened by lead shields. The screening probably was adequate since Mrs. K. could recall no changes in her menstrual records during or after the radiation.

With six years' absence of recurrence, and with no evidence of ovarian dysfunction, there seemed to be no sound basis for concern. Mrs. K. had been warned that pregnancy would be extremely hazardous. When she was assured that this was improbable, she happily accepted her condition, and was delivered on Nov. 20, 1951.

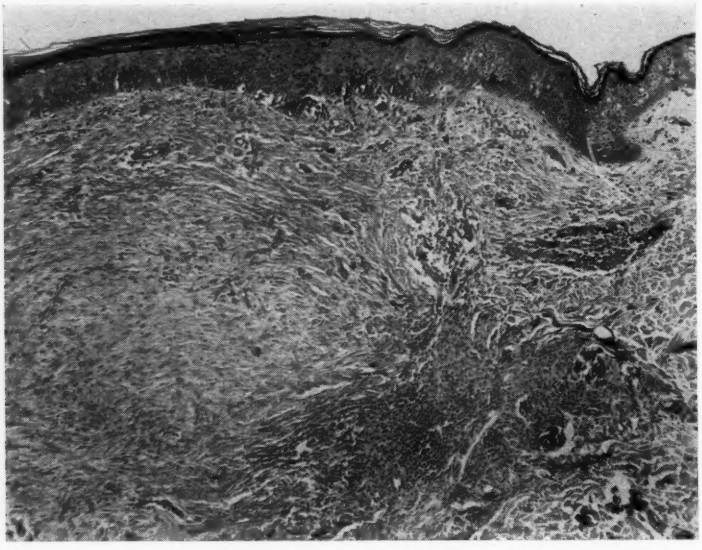

Fig. 13.—Melanoblastoma, junctional type.

Melanoma

The melanomas ordinarily are highly malignant, and recurrences are often rapid and widespread.

Mrs. L. L., a patient of Dr. Donald G. Tollefson, was fortunate in that her recurrence was promptly noted and promptly and thoroughly eradicated. When she was 34 years old, a dark-colored papilloma on the shoulder was removed July 23, 1947, with the use of electrocautery. Almost at once a nevus recurred at the edge of the scar. This was removed surgically on Aug. 4, 1947, and the tissue studied carefully. When early nevocarcinoma was shown, slides were sent to Dr. Carl V. Weller at Ann Arbor. He advised wider excision on the basis of malignant melanoblastoma of junctional type. Accordingly, on Oct. 17, 1947, block

excision of skin and subcutaneous tissue and deep fascia for several centimeters around the scar area was performed and the axillary glands on that side were removed. No metastases were found, and no recurrence has been noted subsequently. She became pregnant within a year and was delivered on Feb. 5, 1949. No further pregnancies have occurred.

Summary

Here, then, is a report of ten women who had cancers and still were able to become pregnant. Only one was so incapacitated by her treatment as to be unable to deliver. In no instance was the mode of delivery influenced by the treatment of the cancer, except that one pelvis was deformed by the loss, at an early age, of an entire leg. Obstetrically, the most complex problem was the delivery of the patient with no rectum or anus, and with extensive scarring of the pelvic tissues. That vaginal delivery was accomplished successfully is a tribute to the skill of the surgeon, the obstetrician, and especially to the forces of Nature.

I do not anticipate that much will be learned from this report beyond the bare fact that, in a woman of suitable age, childbearing may not be rendered impossible after cancer has been detected and obliterated. When, under these conditions, a patient presents herself, very probably she will be much disturbed over her prospects, since she will have been forewarned that her "cure" may fade into recurrence during or after the pregnancy. When there seems a reasonable certainty that the malignancy has been conquered, then the patient should be assured that she is undertaking no additional hazard. I offer no arguments against therapeutic abortion when the time "at risk" has been brief, but, even under such circumstances, each pregnancy must be viewed and conducted according to its own merits and conditions. So far as this particular list is concerned, the high estrogen levels of pregnancy seem to have had no carcinogenic potentialities.

Above all, it would be most unfortunate if this report should be taken as a plea for less thorough treatment of malignancy.

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Discussion

DR. CARL HENRY DAVIS, Miami, Fla.—Dr. Thompson has presented a unique group of cases, and at the same time has reminded us that it is not always necessary for a woman with a severe disabling disease to forego motherhood.

I have had one young woman develop a cancer of the breast soon after delivery. After surgery, I followed her until I left Milwaukee at which time she had no evidence of recurrence. Her sex function was not destroyed, even though some have in the past advocated that women with cancer of the breast have the ovaries removed or their reproductive function destroyed with irradiation. I would not, however, favor a partial operation when a papillary tumor of an ovary is found, even though many partial operations have not been followed by a growth in the other ovary.

As Dr. Thompson states, the treatment of any malignancy must be so radical that few women will later have any possibility of a pregnancy, yet today we are confronted with many diagnoses of cancer in situ in relatively young women who desire children. In this group, I favor ring biopsy with the cold knife, followed by thorough cauterization or coagulation of the cervical tissue. If serial sections or semiserial sections show no evidence of invasion, these young women can be followed with frequently repeated cytology studies and given a chance to have the satisfaction of motherhood. Where cancer in situ is diagnosed during pregnancy, extensive conization of the cervix may be performed with only moderate risk of causing an abortion. The tissue can be thoroughly studied, and following healing cytology studies will show whether or not abnormal cells continue. In a 1952 discussion I reported such a case. The patient was delivered at term by a cesarean hysterectomy as she was past 40.

DR. J. P. PRATT, Detroit, Mich.—When this title was discussed with my surgical colleagues, they reported briefly on three such occurrences which may be added to Dr. Thompson's list.

The first patient had a radical mastectomy for carcinoma in December, 1934, at the age of 32. Prior to the operation she had borne a child at the age of 25 and another at the age of 27. Since the operation there has been no evidence of recurrence. She bore another child at the age of 41 and still another at the age of 44.

The second patient, a 38-year-old spinster, was operated upon in 1946 for cancer of the breast. In 1948 the other breast was removed for chronic cystic mastitis. She was married in 1948. In 1949 she became pregnant. On account of the previous malignancy, interruption of pregnancy was suggested to her by her physician. She refused this advice. She gave birth to a normal child and remained free of recurrence for 7 years.

These 2 patients developed carcinoma of the breast in the fourth decade of life, and their subsequent record shows a five year, or longer, freedom from recurrence. This is in contrast to the third patient who was married in 1944 at the age of 19. Her first child was delivered one year later. She subsequently had 3 spontaneous abortions and delivered her second child in 1948. In 1949, 5 months following the birth of her second child, a mass was noted in the left breast. Her husband was in the Air Force, so she went to an army hospital and had a radical mastectomy. At that time no metastases were reported. Upon discharge from the hospital she was advised not to become pregnant. She returned for deep x-ray therapy and in May, 1949, three months after the operation, she was noted to be approximately 3 months pregnant, and delivered a normal child in January, 1950. During the hospitalization for this child there was no evidence of metastasis. She returned to the army hospital in November, 1951, again approximately 3 months pregnant. She complained of back pain. X-ray and biopsy revealed a metastatic carcinoma of the ninth dorsal vertebra. While in the hospital she aborted spontaneously. She was treated with deep x-ray and androgens. During this period of treatment she was advised to have removal of both ovaries to which she reluctantly consented. She improved following treatment and at the present has no back pain. An osteolytic lesion of the left hip was shown by x-ray in June, 1953. At the present time her outlook is pleasant and hopeful, and she believes her prognosis is fairly good.

The occurrence of carcinoma of the breast relatively early in the reproductive period creates special problems. One of these problems is that at this age the incidence of recurrence is high and the rate of growth of the original lesion is usually rapid. Ovarian function has been assigned varying degrees of responsibility for growth of cancer. For this reason the obstetrician and gynecologist is often called upon to express an opinion as to the desirability of removing or destroying the ovaries. In such a consideration he is soon aware that it is not merely an academic question.

Bearing children is fundamental in the lives of most women. When a woman is presented with the facts that removal of the ovaries might prolong her life but would take away from her the opportunity of pregnancy, she is very likely to take the risk and decide to retain her ability to reproduce. When a malignancy is known to be hopeless as far as cure

is concerned, the greatest obligation of the physician is to give the patient hope and comfort. I recall one patient who came to us with spontaneous fracture of the spine due to metastatic carcinoma of the breast. She was paralyzed from the waist down. She was three months pregnant. This gave her great happiness and she went home to her little country town where she died before the baby was viable. That pregnancy gave her a great deal of comfort in her last days of life. To have interrupted her pregnancy would have taken away her greatest hope and pleasure. This indeed is a special problem to be met in consideration of the treatment of patients with carcinoma of the breast.

Dr. Thompson's observation that the high level of estrogenic activity showed no carcinogenic effect, confirms the impression generally held today. The characteristic effect of estrogen is to promote growth of cells that are susceptible to the influence of estrogen. That does not indicate that estrogens cause cancer or that they cause metastasis.

The problems presented here today offer a real challenge to physicians from an academic and social point of view.

DR. FRANK R. SMITH, New York, N. Y.—I am impressed with several things in Dr. Thompson's paper. One is the doubtful diagnosis in several of these patients.

When you try to go through the literature and find any group of patients who have had malignant lesions associated with pregnancy, it is very hard to collect a group of any size. Some years ago we tried to investigate this problem at Memorial Hospital, and over a period of ten years, having the cooperation of other men, I was able to collect only 54 patients with any type of cancer and coincidental pregnancy.

Twenty-two of these were patients with cancer of the breast. Some were patients who were pregnant while they had the cancer, and some were patients who had pregnancies afterward. I was convinced, after studying that small number of cases, that patients with cancers of the breast discovered when they are pregnant do equally well or better if the cancer is treated and the pregnancy allowed to continue. There appears to be a rapid increase in the tumor immediately following the termination of pregnancy, whether it is at term or during the early months. Patients who had had the breast removed and then later became pregnant also did equally well if the pregnancy was not interrupted, provided an empirical time of two years had elapsed.

I was interested in the two cases of intestinal cancer which were reported, and also the ovarian cancer. Treatment should, I think, depend on the grade of malignancy of those tumors. I was disappointed that they did not let the girl with the low colostomy go on with her pregnancy, and I would like to ask why, if Dr. Thompson felt it was necessary to terminate the pregnancy, he did not sterilize her to protect her against the second pregnancy?

DR. HERBERT E. SCHMITZ, Chicago, Ill.—I fear that this report may be interpreted by some as evidence that it is permissible to encourage pregnancy following the apparently successful treatment of malignant disease. I would suggest, therefore, that we review the cases that Dr. Thompson has reported this morning. Two had sarcoma of the extremity when extremely young, and I am quite sure that we are all in agreement that, had the amputation not been successful, these patients would not have gone on to puberty or to the childbearing period. As we all know, these youngsters frequently have unrecognizable pulmonary metastases before the amputation is carried out, and die within one year to 18 months. Therefore, in these two instances we had patients definitely cured of their disease, not with arrested diesase, and pregnancy brought about no problem.

As for the patient with the breast lesion, the highest incidence of survival is in those patients with localized, very early lesions, without any nodal extension demonstrable—not on the examination of one or two nodes alone, but by a very careful sectioning of all of the nodes removed. Here again we would expect to have an arrest in that patient, and pregnancy would not be too big a problem.

However, in invasive carcinoma, especially with nodal metastasis, I believe we all agree that pregnancy would be a very hazardous undertaking, and I for one would object to my patient becoming pregnant.

As to the question of pregnancy in the presence of a carcinoma of the melanotic type: Too few of these patients remain free of disease after the extensive block dissection that George Pack is doing at the present time without the additional irritation of pregnancy. Therefore, I would not have the fortitude to permit a patient with a melanotic carcinoma to undertake a pregnancy.

The treatment of the ovarian lesions is debatable. Only a day or two ago Dr. Brewer said to me, "I would like to be able to tell which papillary lesions of the ovary are malignant and which are benign, and I would like to follow those patients over many years to determine the correctness of the diagnosis." I am in full agreement with Dr. Brewer.

As to the management of carcinoma of the breast that complicates pregnancy: It has been our experience during the past ten years, since we first reported on this method of treatment, that those patients whose pregnancies were carried, as Dr. Smith said, to viability and terminated by section, with immediate removal of the ovaries, had marked regression of the tumor. I think, therefore, that further therapy with the male hormone substantiates the fact that the removal of the ovary plus the use of the male hormone is acceptable treatment. I would advise that, in those patients suffering from breast cancer, we perform oophorectomy, not to sterilize the patient in order to preclude future pregnancies, but as a means of treatment of the disease.

DR. THOMPSON (Closing).—In answer to Dr. Smith's last question as to the reasons for not sterilizing the patient with rectal carcinoma, I should add that she was a widow and I did not realize that she would marry within a few months and again become pregnant. Even if I had known this, I would have been very hesitant to open that abdomen on account of the adhesions. The second pregnancy, after she had married, was terminated. Then the husband when he was advised that further pregnancies were out of the question had a vasectomy performed.

In the other patient with rectal carcinoma, an interesting point was that the surgeon attempted to sterilize her at the time of the combined procedure by burying the fimbriated ends of the tubes underneath the new pelvic peritonization covering of the lower abdomen. In spite of that, she proceeded to get pregnant and carried to term, as related.

I quite agree with Dr. Schmitz that these women should not be encouraged to become pregnant. Occasionally they do, however, and then the question arises as to what we are going to do. If the time "at risk" is not too short, it is reasonable to permit them to go on and carry out their reproductive function, which is usually their ambition. They have been told that pregnancy should not be undertaken, but when it has occurred a therapeutic abortion may be a most depressing situation for them to confront. They need support; they need the encouragement that can be given them when you can offer that encouragement logically and with mental assurance to yourself.

THE ROLE OF ANTIBIOTICS IN THE MANAGEMENT OF INCOMPLETE ABORTIONS*

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THE seriousness of incomplete abortion with its complications has been reflected in all maternal mortality studies. The records of these studies indicate a declining morbidity and mortality rate due to abortions. This has been achieved by efforts directed toward replacement of lost blood, prevention and control of infection, and early emptying of the uterus when the abortion was incomplete. Hemorrhage, though often alarming, is rarely the cause of maternal death, while infection, when present and uncontrolled, is commonly the source of dysfunction, disability, and occasionally death. Evacuation of the uterus is the most effective means of reducing hemorrhage, but much disagreement has been expressed as to how and when this procedure should be attempted. Prevention and control of infection remain our most important consideration in improved management of the incomplete abortion. In the last decade the advent of sulfonamides and antibiotics has given us new weapons with which infection can be more adequately controlled. Ostergaard,[1] Webster,[2] and Collins[3] have reported improvement in the management of abortion with these drugs. Falk and Abelow[4] advocate a more active surgical approach toward the problem after the use of chemotherapy and antibiotics.

Material

To determine the role of antibiotics in the management of abortions, 946 consecutive patients with incomplete abortions, admitted to Jefferson-Hillman Hospital from 1943 to 1952, were studied. There were 741 cases without infection and 203 cases with infection. Only hospitalized patients were used in this study. Many more patients with abortions came to the emergency room, were examined, given antibiotics and oxytocics, kept under observation for 4 to 6 hours, classified as having complete and uninfected abortions, and sent home. An abortion was classified as incomplete when a pregnancy of twenty weeks or less had been partially terminated. This was determined by the finding of tissue in the lower genital tract on examination or by removal of placental tissue surgically.

The time that antibacterial drugs were available and used resulted in a study of the admitted cases in three groups (Table IA). The first, designated as Group A, 340 cases, admitted 1943-1945, was treated with sulfonamides.

*Presented at the Sixty-fourth Annual Meeting of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons, Hot Springs, Va., Sept. 10, 11, and 12, 1953.

The second, designated as Group B, 282 cases, admitted 1946-1948, was treated with sulfonamides and/or penicillin. The third, designated as Group C, 324 cases, was admitted 1949-1952 and treated with sulfonamides plus penicillin as the only antibiotic, or with a combination of penicillin and streptomycin, aureomycin, or Chloromyectin as indicated clinically or by cultures and sensitivity determinations.

TABLE IA. DISTRIBUTION OF 946 CONSECUTIVE INCOMPLETE ABORTIONS ACCORDING TO YEAR OF ADMISSION

	NO. OF CASES	SEPTIC	
		NO.	PER CENT
Group A 1943-1945	340	78	22.9
Group B 1946-1948	282	56	19.8
Group C 1949-1952	324	71	21.9

Prophylactic Role of Antibiotics

Our data do not give a clear picture of prevention of infection in incomplete abortions. In the 741 uninfected cases antibiotics were given to 308 on admission, while 433 did not receive the drugs. Many of the latter group were admitted before penicillin became available. No uninfected case became infected after admission regardless of drug administration. It appears that, if blood loss is controlled in aseptic cases and the uterus promptly evacuated, antibiotics should be unnecessary. The incidence of puerperal infection, however, can be reduced in term pregnancy with long labors and ruptured membranes by the use of these drugs. Thus, it is to be expected that the incidence of sepsis in abortions should also be lessened, since the infecting organisms are usually the same. The medicine must be given early and other principles of therapy promptly applied. First among these principles should be blood replacement. Approximately 35 per cent of our cases have required transfusion. At present, all patients with incomplete abortions receive penicillin (a total of 1.5 million units in 24 hours) on admission, since the number of induced abortions, symptoms of infection, or amount of previous therapy cannot be reliably determined by history. Therapeutic dosage of antibiotics had not been given once in 205 septic cases prior to admission.

Antibiotics in Infected Abortions

Two hundred five cases of incomplete abortion are classified as infected. The criteria of this clinical diagnosis are:

1. Temperature of 100.4° F. sustained for 24 hours or more in the absence of other possible cause.

2. Foul lochia and tender, enlarged uterus as signs of intrauterine infection.

3. Signs and symptoms of extrauterine infection such as periuterine consolidation, adnexal swelling, tenderness, and loss of uterine mobility on pelvic palpation.

The incidence of infected abortion has varied but little as indicated by Table IA. The degree of advancement and severity of the clinical picture produced by infection in abortions has been classified by us after Burnett,[5] as follows:

Type I: Infection limited to the uterus.

Type II: Extrauterine spread of infection to the structures of pelvic cavity only.

Type III: Cases in which infection has become extrapelvic, such as generalized peritonitis, septicemia, etc.

TABLE IB. TYPES OF TREATMENT EMPLOYED IN THE THREE GROUPS OF CASES

	NO. SEPTIC	ANTIBIOTICS		BLOOD		SURGERY		HOSP. STAY (DAYS)
		NO.	PER CENT	NO.	PER CENT	NO.	PER CENT	
Group A 1943-1945	78	0		40	51.3	11	14.1	13.6
Group B 1946-1948	56	48	85	35	62.5	9	16.0	10.5
Group C 1949-1952	71	71	100	38	53.5	39	54.9	11.8

This arbitrary classification has been very helpful to us in clinical management, the principles of which are illustrated by Table IB. The advancement of infection found in each group of this survey, according to these types, is indicated by Table II.

TABLE II. CLASSIFICATION OF CASES ACCORDING TO DEGREE OF EXTENSION OF INFECTION

	NO. SEPTIC	TYPE I	TYPE II	TYPE III	DEATHS
Group A 1943-1945	78	56	17	5	3
Group B 1946-1948	56	40	13	3	1
Group C 1949-1952	71	50	16	5	2
Total	205	146	46	13	6

On admission the patient with abortion is classified after history and physical examination. The cervical canal is inspected; tissue, if found, is removed with sponge forceps; and cultures are obtained from the cervical canal if the patient is febrile or gives a history of attempts at induction. Blood cultures are requested if the patient has a temperature of 101° F. or gives a history of chills. Bimanual examination is done to determine the extent of involvement and to detect abscess formation if present.

Cervical cultures have helped but little in Type I cases. Usually, patients respond to treatment before culture and sensitivity reports are available. The

infecting organism has been determined with increasing certainty by the culturing of pus or secretions drained by colpotomy, and comparison of this growth with bacteria from cervical culture. Determination of causative bacteria was not always possible even in Type II and Type III cases as indicated by Table III. In the advanced cases with abscess formation and subsequent drainage, however, cultures indicated mixed growth with *Bact. coli* predominating. Pyogenic staphylococci and nonhemolytic streptococci were the second and third most common organisms found, respectively.

Because of the frequency of mixed infections in advanced, incomplete septic abortions, the use of antibiotics in combination is often desirable. One great value of culture has been the detection of gram-negative organisms and the antibiotics to which they are most sensitive. However, clinical experience has shown that in most Type I cases with mixed infections a single antibiotic, preferably penicillin, is all that is necessary. If, after 48 hours of penicillin therapy, clinical response suggests that one antibiotic is insufficient, reports on sensitivity studies should be available to determine which additional antibiotic should be used. Dowling and associates[6] have advocated combination of antibiotics in staphylococcic infections and have emphasized the diminishing frequency of development of resistant strains. In cases diagnosed as Type II or III at the time of admission, combination antibiotics, such as penicillin and aureomycin, should be given initially.

TABLE III. CERVICAL CULTURES IN 205 INFECTED ABORTIONS

PREDOMINATING ORGANISM	TYPE I	TYPE II	TYPE III
Staphylococcus albus	15	2	5
Staphylococcus aureus	12	6	3
Aerobacter aerogenes	3	5	4
Hemolytic streptococcus	16	1	0
Nonhemolytic streptococcus	8	3	2
Anaerobic streptococcus	5	2	0
Bacterium coli	19	15	8
Streptococcus viridans	0	0	1
Proteus	0	0	2
No report or no growth	78	12	4

Effect on Mortality

Table IV indicates that antibiotics have materially assisted in lowering mortality; penicillin in addition to sulfonamides having had the greatest effect, as indicated by the lowering mortality of Group B, compared to Group A. Altemeier and Culbertson[7] reported that in mixed infections one antibiotic usually is complementary to another, thus increasing the range of the bacterial spectrum. They also found that, in a small group, not only may one antibiotic be antagonistic to another, but that, if suppuration continues and pus drainage is delayed, bacterial resistance to the drugs often increases. Thus, the effect of antibiotics on mortality is incomplete, as the result is not only dependent on early administration of the most efficacious antibiotic, but is also linked to timely application of indicated surgery and to blood replacement. Table V shows mortality rates reported recently by other observers for septic abortions.

TABLE IV. MORTALITY RATE IN RELATION TO TYPES OF DELIVERY AND YEARS OF ADMISSION

	SEPTIC	DEATHS	MORTALITY RATE
Group A 1943-1945	78	3	3.84%
Group B 1946-1948	56	1	1.76%
Group C	71	2	2.81%
1949-1952	205	6	2.92%

TABLE V. PREVIOUSLY REPORTED MORTALITY RATES

AUTHOR	NO. SEPTIC	DEATHS	MORTALITY RATE
Ramsay[8]	1430	47	3.29%
Bishop[9]	239	8	3.35%
Studdiford[10]	1579	17	1.08%
Burnett[5]	267	2	0.75%
Jefferson-Hillman	205	6	2.92%

TABLE VI. INFECTED ABORTION—SURGICAL UTERINE EVACUATION

	TYPE I	TYPE II	TYPE III
Group A 1943-1945	7 8.9%	3	0
Group B 1946-1948	2 3.6%	2	0
Group C 1949-1952	27 54%	4	0

Discussion of Deaths

There were six deaths all of patients who were infected. Autopsy is obtained by permission of the family of the deceased; consequently, only two are available. A brief discussion of each death with reference to antibacterial drugs follows:

CASE 1.—This 28-year-old Negro woman was admitted in January, 1943, and died on the thirteenth hospital day. No autopsy was granted. The history was that of 12 weeks' gestation with abdominal cramps, vaginal bleeding, chills and fever for 2 weeks before admission. Placental tissue was removed from the cervix. Cultures were obtained but organisms not determined. A clinical diagnosis of incomplete abortion, generalized peritonitis, and pelvic abscess was made, and she was treated with sulfonamides, oxytocics, blood, oxygen, and intravenous fluids.

Comment.—Early and adequate antibacterial therapy with drainage of the abscess was lacking in the management of this case. The causative organism was not determined.

CASE 2.—B. L. A., a 19-year-old white woman, was admitted in 1943 after the second attempt at criminal abortion. She gave a history of chills and fever for ten days, vaginal bleeding for 2 weeks, swelling in the right leg, and cough productive of phlegm without blood. The clinical diagnosis was infected, incomplete abortion, Type III; thrombophlebitis, right leg; and septic emboli to the lungs. Blood culture showed no growth. Treatment consisted of sulfonamides, blood, oxygen, and right lumbar sympathetic block. Respiration gradually became more difficult, and the patient died on the twelfth hospital day. Permission for autopsy was not obtained.

Comment.—Early, adequate antibiotics and/or vena cava ligation might have prevented this death.

CASE 3.—A 32-year-old white woman, who was admitted in 1945, gave a history of chills and fever, abdominal pain, and vaginal bleeding of one week's duration. The clinical diagnosis was septic abortion with generalized peritonitis. Sulfonamides, intravenous fluids, blood, and Wangensteen drainage were given. The patient died on the twenty-fifth hospital day. Diagnosis at autopsy was retained placental tissue, chronic endometritis, bilateral suppurative salpingo-oophoritis, purulent peritonitis with widespread abscess formation. Organisms cultured from abdominal fluid were streptococci and staphylococci.

Comment.—Antibacterial drugs were given late and were insufficient for mixed infections. After the patient had shown no improvement, abdominal exploration and drainage might have been helpful.

CASE 4.—This 18-year-old Negro girl was admitted in 1947 and died on the fifty-eighth hospital day. No autopsy was done. She gave a history of criminal abortion 5 days before admission and had a febrile course with chills. Blood culture showed no growth. Colpotomy was done on the eleventh hospital day and ten days later jaundice developed. Culture of pus from the abscess grew *Staphylococcus albus* and diphtheroids. The clinical diagnosis was incomplete abortion, pelvic abscess, pelvic peritonitis, and toxic hepatitis. Treatment was triple sulfonamides, penicillin, streptomycin, whole blood, as well as colpotomy.

Comment.—Death was probably due to a resistant *Staphylococcus albus* organism. Abdominal exploration and drainage early in the course of the disease, or other antibiotics, possibly would have helped.

CASE 5.—R. P., a 34-year-old Negro woman, was admitted in 1950 after abortion of a sixteen-week fetus. The history was that of chills and fever, vaginal bleeding, and abdominal pain. She was in another hospital for 6 days before transfer. The diagnosis on admission was septic, incomplete abortion and generalized peritonitis. Cervical cultures were reported as beta hemolytic streptococci, *Escherichia coli,* and Proteus. Penicillin, sulfonamides, and streptomycin were used in the treatment of this patient. She improved but went into shock on the seventh hospital day and died. Autopsy showed postabortal endometritis, thrombi and abscesses in the myometrium, and peritonitis with ruptured pelvic abscess. Culture of pus from the abdomen grew gram-positive cocci and gram-positive rods.

Comment.—Failure to recognize a pelvic abscess with lack of adequate drainage were important contributing factors in this maternal death.

CASE 6.—This 23-year-old Negro woman was admitted in 1951 and died on the second hospital day. She had had fever for 9 days before admission. Incomplete abortion, pelvic abscess, and peritonitis were the clinical diagnoses. On the day of admission 1,000 c.c. of pus was evacuated by a posterior colpotomy and Proteus grew on culture. Treatment consisted of sulfathiazole, penicillin, and aureomycin. The patient was moribund on admission and her condition remained unchanged. Autopsy was not granted.

Comment.—The patient had adequate therapy but too late.

Antibiotics and Surgery

In the septic, incomplete abortion the clinical practice has been not to empty the uterus surgically unless hemorrhage requires it. Webster[2] reports that, with chemotherapy and antibiotics, evacuation of the uterus in the afebrile, incomplete abortion is without danger. She reports an abortion mortality rate of 0.11 per cent. Burnett[5] reports an abortion mortality rate of 0.09 per cent in 2,322 cases and a septic abortion mortality rate of 0.75 per cent in 267 cases. Surgical evacuation of the uterus was done by Burnett in 215 (93 per cent) of 267 septic cases. Table VI shows an increasing incidence

of surgical evacuation of the uterus under cover of antibiotics. This, we believe, is a safe procedure for Type I cases. The preference is to evacuate the uterus after the patient has become afebrile and has remained so for at least 24 to 48 hours—and then only if the patient continues to bleed excessively or if there is evidence that the abortion remains incomplete. No Type I case, surgically evacuated, progressed in severity.

The practice of surgical drainage for pus accumulation continues to be necessary. This should be done without delay to prevent bacterial resistance to antibiotics, as well as to limit further spread of infection. Even in cases of generalized peritonitis, which have not responded to antibiotics and blood, exploration with drainage of the abdominal cavity or abscesses may become necessary. This has been done in three cases and resulted in recovery of all three patients. Total hysterectomy was performed in three other patients who had Type I pelvic infection and uterine fibroids, and no advancement of the inflammatory process was noted postoperatively. Vena cava ligation was not done in any cases, although femoral vein ligation became necessary in one patient. Except when thrombophlebitis and embolus are complications, death usually occurs from peritonitis and septicemia. We have found that antibiotics can be used for control and localization of infection, and, if followed by surgery when indicated, will reduce maternal deaths from infected abortion.

Summary

1. Review of 946 consecutive incomplete abortions is made with respect to the role of antibiotics in the management. Infection was present in 205 cases and absent in 741.

2. Infected abortions are arbitrarily classified into three types, dependent on advancement of infection.

3. The role of antibiotics in uninfected cases is not determined but is considered to be advantageous.

4. Antibiotics, administered early, lower mortality and morbidity rates and reduce hospital stay. With antibiotics, surgical evacuation of the uterus can be done safely when infection is limited to the uterus. A more aggressive approach to surgical exploration and abscess drainage can be taken in advanced infections, even in generalized peritonitis, when antibiotics are given.

5. From cultures, *Bact. coli,* staphylococci, and hemolytic streptococci are found to be more common in mixed infections.

6. A septic abortion mortality rate of 2.94 per cent and an over-all mortality rate of 0.63 per cent for incomplete abortion was obtained.

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Discussion

DR. L. MARSHALL HARRIS, Newport, R. I.—A review of Dr. Jones' paper indicates, from the material studied and the statistics presented, that his observations are made on a varied time scale extending from 1943 to 1953. This period covers the advent of the use of chemotherapeutic agents in obstetrics and gynecology through the antibiotic therapy. His criteria for clinical diagnosis, classification, and management of infected incomplete abortion are noteworthy and demonstrate a significant variety of stages of severity of infection as well as degree of pelvic involvement.

The significance of sequelae, or perhaps better, the residual pelvic pathology of postabortal infections manifested by our so-called pelvic inflammatory lesions, seems to indicate certain important requirements in the management of these cases. These include early hospitalization and examination of threatened inevitable and incomplete abortion. Early diagnostic studies upon admission must include complete history and physical examination, complete blood count, culture from the cervix when practicable, sedimentation rate, provision of blood for transfusion of the patient and perineal preparation. In our opinion early administration of antibiotic therapy combined with chemotherapy when the history and findings require such preventive measures reduces morbidity and mortality. We do not hesitate to institute prophylactic antibiotic agents in these cases when they are considered to be indicated.

On the basis of experience in our Naval hospitals, the objective toward prevention and control of infection and complications requires the accomplishment of the previously mentioned procedures in preparation for early evacuation of the uterus when it is appropriate and practical. This method of management is mentioned in Dr. Jones' paper. Fortunately for patients and staff, the author's cases classified as "Type II and Type III" constitute a relatively small percentage of cases seen on our service. Therefore, as shown by the author's statistics, our experiences in the Type III cases has been limited on the Services of three Naval hospitals during the past seven years. This we attribute to a rather well-controlled antenatal clinic, the availability of penicillin, streptomycin and other antibacterial agents, with facilities for early hospitalization, evaluation, and active treatment. The essayist has covered the management of the severe infections which require more intensive and definitive treatment with drainage, major surgery in the more severe cases, and prolonged hospitalization.

The matter of therapeutic approach in the management of incomplete abortion is predicated to a great extent upon an early diagnosis. This usually depends upon how early the patient is seen.

Mortality in the author's series is stated as 6 deaths (0.6 per cent). It is logical that these may have been associated with patient delay in reporting for treatment, while other factors may have been involved.

As stated before, rather satisfactory control is possible on our Services to permit early diagnosis and treatment. Therefore, we are unable to report on extensive complications (Type III classification). Undoubtedly, for the same reason we do not have any deaths to report to date as a result of incomplete abortion over a seven-year period, with a total of 1,126 cases, of which 524 were infected upon admission.

We believe early and adequate antibiotic treatment, blood transfusion, and evacuation of the uterus definitely lower the incidence and extent of postabortal residual pathology. We believe this also holds true in postpartum pelvic infection.

The factors which seem to influence the extent of infection in incomplete abortions may be listed as follows:

1. The type of antenatal care and its course, to include recognition of pre-existing pelvic lesions, anemia, and general health of the patient.

2. The time interval between the onset of signs and symptoms of threatened, inevitable, or incomplete abortion and hospitalization of the patient.

3. The period of gestation, status of the membranes and cervix, and amount of blood loss since onset. These factors also influence the management of the case.

To reiterate, the policy which is currently followed, once the patient is admitted, includes: (1) early evaluation of the status of the cervix, membranes, and products of conception; (2) culture from the cervix, if practicable, and determination of extent of the infection by pelvic examination, complete blood count and other laboratory studies having been done upon admission of the patient; (3) institution of combined antibiotic therapy and chemotherapy, depending upon the extent of infection, and supportive measures to include blood transfusion when indicated; (4) preparation of the perineum for surgical evacuation of the uterus as early as possible. This procedure should be carried out preferably in the operating room under anesthetic. Pentothal Sodium has been the anesthetic of choice. Oxytocics are to be given at the discretion of the operator. On our service the Pitocin drip has served the purpose rather well, especially following dilatation and curettage. It is started prior to sharp curettage in those patients in whom such a procedure is indicated.

The opportunity to review Dr. Jones' excellent study has emphasized the fact that the problem of management of incomplete abortions is not completely solved. His frank and logical presentation should stimulate research and promote vigilance in the practice of preventive obstetrics.

The work of Drs. Eastman, Douglas, and other Fellows of this association, pertaining to the use of antibiotic and chemotherapy is recorded in the literature over the past ten years and remains fundamentally the basis for their role in obstetrics and gynecology.

DR. JONES (Closing).—Dr. Harris reports a series of cases of abortion of similar size to ours without a death. However, in his series there are no advanced septic abortions, and all of his cases came under medical management early. This emphasizes the importance of time factors in the prevention of mortality. Obviously, early management of the abortion cases with our present armamentarium of antibiotics, oxytocics, blood, and indicated surgery will reduce mortality to almost nil.

THE MANAGEMENT OF PREGNANCY COMPLICATED BY HEART DISEASE*

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(From the Pennsylvania Hospital)

THE management of pregnancy complicated by heart disease constitutes one of the great challenges in obstetrics. During the past decade notable advances have been made in the obstetric and medical treatment of this condition, and a rich literature has accumulated. However, even more study is indicated, as the mortality rate of heart disease in pregnancy still accounts for a substantial proportion of maternal and fetal deaths. Further, the part played in maternal mortality by heart disease grows proportionately larger due to the spectacular decrease of deaths from other causes. This has been confirmed by Eastman (1937) who states that only sepsis and toxemia claim more lives during pregnancy and the puerperium; and by Jensen (1938), who believes that heart disease is fourth or fifth among the causes of maternal mortality, and is possibly the greatest cause of death during labor and the puerperium. Stander (1942) found in his series that heart disease was responsible for 10.4 per cent of all maternal deaths. In the Pennsylvania Hospital during 1937-1952, heart disease has been the greatest single cause of death during pregnancy and the puerperium (Fig. 1).

The obstetrician is usually the first physician to see the patient in early pregnancy. In taking her history and performing a physical examination at the initial antepartum visit, he learns of the presence of heart disease. In addition to studying the patient from the obstetric standpoint, he must determine the nature of the cardiac lesion, evaluate its severity, and estimate the risk entailed by pregnancy. Adequate supervision of the cardiac condition is essential so that compensation may be maintained. Advice should be given concerning activity, rest, proper diet, and prevention and treatment of infections.

Supervision is essential throughout pregnancy, delivery, and the puerperium if the risk of pregnancy in heart disease is to be reduced to a minimum. The responsibility is great and the best results are obtained by sharing the care of the patient during these periods with a competent cardiologist. Close liaison and frequent consultation between the obstetrician and cardiologist reduce the hazards to both mother and baby.

An analysis of cases of cardiac disease occurring in pregnancy serves as the best basis for determining the proper management of these patients. This study is based upon the pregnancies complicated by cardiac disease which occurred in the Pennsylvania Hospital during a sixteen-year period (1937 to 1952, inclusive). The results of the clinical experiences and the treatment are summarized.

*Presented at the Sixty-fourth Annual Meeting of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons, Hot Springs, Va., Sept. 10, 11, and 12, 1953.

The discussion is divided into two parts. The first includes all cardiac-obstetric patients who were treated in the Out-Patient Clinic and Hospital from 1937 to 1952, inclusive. In the second part, the cases are divided into two groups, those treated from 1937 to 1947, and those treated from 1948 to 1952. The reason for this division is to analyze the management and results since the installation of the Cardiac-Obstetric Clinic in 1948. Previous to this date cardiac-obstetric patients were seen at different times by the cardiologist and the obstetrician. This often resulted in delay, loss of records, broken appointments, and poor follow-up of patients with broken appointments.

Records on 565 pregnancies complicated by heart disease in the period from Jan. 1, 1937, to Jan. 1, 1953, were available for study. During this time 41,361 deliveries occurred in the hospital. This represents an incidence of 1.12 per cent of heart disease in pregnancy, and corresponds to the 1.7 per cent given by Hamilton, and the 1.27 per cent of Jensen. It is higher than the 0.8 per cent given by MacRae of the Queen Charlotte Hospital of London, but lower than the 2.3 per cent found by Stander.

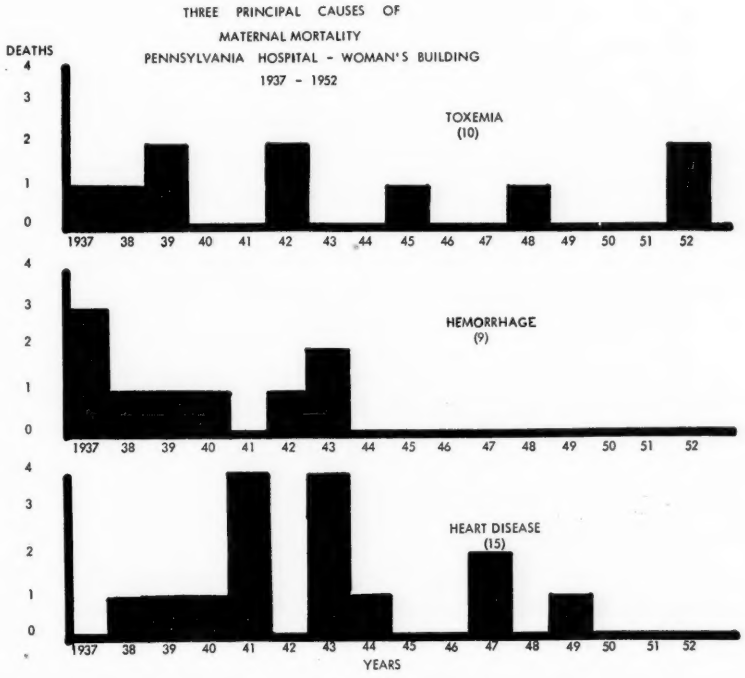

Fig. 1.—The three principal causes of maternal mortality at Pennsylvania Hospital, 1937 to 1952, inclusive.

No patients with pre-eclampsia or eclampsia are included in the analysis, and hypertensive cardiovascular disease is included only if there is present a history of prolonged hypertension prior to pregnancy and blood pressure studies for at least one week post partum showed a systolic level of 140 mm. Hg and a diastolic level of at least 85 mm. Hg. All of the patients were under the cardiac

supervision of Dr. Joseph B. Vander Veer, Chief of the Division of Cardiology of the Pennsylvania Hospital, or his associates. The obstetrical supervision was given by all the members of the Division of Obstetrics and Gynecology.

Period 1937-1952

An analysis of the various types of heart disease over the sixteen-year period is shown in Table I.

TABLE I. ETIOLOGICAL TYPES OF HEART DISEASE AMONG 41,361 PREGNANT WOMEN, 1937-1952

ETIOLOGY	NO. OF CASES
Rheumatic heart disease	461
Hypertensive cardiovascular disease	62
Congenital heart disease	26
Acute bacterial endocarditis	2
Syphilitic heart disease	1
Acute pericarditis	1
Arteriosclerotic heart disease	1
Miscellaneous*	11
Total	565

*Paroxysmal tachycardia, hyperthyroidism, hypothyroidism.

Digitalis Therapy and Functional Capacity.—

Seventy-six (13.8 per cent) of this series of 565 patients showed symptoms and signs of various degrees of cardiac failure when first seen, and were immediately placed on digitalis therapy. Ninety-five other patients received digitalis therapy during the course of their pregnancy. Thus almost one-third (3.1 per cent) of all of our patients received digitalis therapy.

The distribution of these patients in this series among the four functional classes and the number of patients in each class who were digitalized are shown in Table II.

TABLE II. DISTRIBUTION OF PATIENTS WITH HEART DISEASE AMONG THE FOUR FUNCTIONAL CLASSES

	CLASS 1	CLASS 2	CLASS 3	CLASS 4
Total number of cases	274	215	60	16
Number of patients digitalized	5	90	60	16

Digitalis therapy should be freely used and is indicated if any signs of impending failure are present. We believe it will do much to lower the incidence of acute congestive failure.

Maternal Mortality in Pregnancy With Heart Disease.—

TABLE III. MATERNAL DEATHS RESULTING FROM CARDIAC AND NONCARDIAC CAUSES, 1937 TO 1952 INCLUSIVE

Total number of pregnant women delivered in the hospital		41,361
Total number of maternal deaths (cardiac and noncardiac)		55
Maternal mortality (all causes)		0.13%
Maternal deaths of cardiac origin	(15)	0.03%

TABLE IV. MATERNAL MORTALITY RATE OF PREGNANT PATIENTS WITH HEART DISEASE ACCORDING TO FUNCTIONAL CLASSES

Total number of cases studied	565	
Total number of deaths among cardiac patients	15	
a. Number of deaths in functional Classes 1 and 2		3
b. Number of deaths in functional Classes 3 and 4		12
Maternal mortality rate among pregnant cardiac patients	2.6%	

The causes of death of the pregnant women with heart disease are summarized in Table V.

TABLE V. CAUSES OF MATERNAL DEATH AMONG 565 PREGNANT WOMEN WITH HEART DISEASE

CAUSES OF MATERNAL DEATH	NO. OF CASES
Acute congestive failure	6
Acute congestive failure with pneumonia	4
Acute bacterial endocarditis	2
Acute congestive failure and rupture of aorta	1
Acute exacerbation of rheumatic endocarditis	1
Pulmonary embolism	1
Total	15

As observed from Table V, the principal cause of death was acute congestive failure with or without pneumonia. Acute infections were responsible for 7 of the 15 deaths. These often precipitated the acute congestive failure. They occurred prior to 1948, before antibiotics were used as effective therapeutic agents for the control of infections. In all, 11 patients died between the seventh and eighth months of pregnancy, the period in pregnancy of the heaviest load on the heart. Three patients showed signs of failure after delivery and died six to forty hours after delivery.

Fetal Mortality.—

Table VI presents the causes of fetal mortality that occurred in these 565 cases. There was a total of 70 fetal deaths with a mortality of 12.3 per cent. Included in these deaths are 14 abortions and 6 postmortem cesarean sections.

TABLE VI. THE ETIOLOGICAL FACTORS CONCERNED WITH FETAL MORTALITY IN 565 PATIENTS WITH HEART DISEASE

CAUSES OF FETAL DEATH	NO. OF CASES
Prematurity	27
Undelivered (including 6 postmortem sections)	9
Spontaneous abortions and dilatation and evacuation	14
Miscellaneous (including pulmonary edema, atelectasis, congenital heart disease)	20
Total fetal deaths	70
Fetal mortality in cardiac patients	12.3%

Prematurity was the most frequent cause of fetal death. The high mortality rate present is consistent with rates reported by Hamilton, Teel and Clifford, who also found prematurity causing the greatest number of deaths in pregnancy with heart disease.

Types of Delivery and Anesthesia.—

Tables VII and VIII show the types of delivery employed and their relation to maternal and fetal deaths. As shown, 281 cases, almost one-half (49.8 per

cent), were delivered by the low forceps method. This was done principally to shorten the second stage of labor and to prevent undue straining and exhaustion of the patient at this time. It was performed only when the cervix was completely dilated and all the conditions were present for the safe and successful application of forceps.

TABLE VII. METHODS USED FOR DELIVERY OR TERMINATION OF PREGNANCY IN 565 PATIENTS WITH HEART DISEASE

METHOD	NO. OF CASES
Low forceps	281
Midforceps	4
Spontaneous delivery	136
Cesarean section	88
Hysterotomy and evacuation	16
Breech extraction	11
Undelivered (including 6 postmortem sections)	9
Spontaneous abortions	10
Dilatation and evacuation	10
Version (second of twins)	1
Total	566

The correlation between maternal and fetal deaths in Table VIII does not indicate any relative degree of safety for any particular method of delivery. In the fifteen maternal deaths, no major operative procedures were used. The acute congestive failure cases in the late months of pregnancy were treated conservatively. Sixty-six per cent, or two-thirds of the cesarean sections, were performed for obstetrical indications. All but one of the remaining 33 per cent cesarean section deliveries primarily for heart disease were performed in the early years of this study, 1937 to 1944. There were no maternal deaths in the 104 abdominal deliveries which comprised 88 cesarean sections and 16 abdominal hysterotomies.

TABLE VIII. CORRELATION OF MATERNAL MORTALITY AND FETAL DEATHS WITH METHOD USED TO TERMINATE PREGNANCY

METHOD	MATERNAL DEATHS	FETAL DEATHS
Low forceps	3	3
Midforceps	0	0
Spontaneous delivery	2	18
Cesarean section	0	7
Hysterotomy and evacuation	0	12
Breech extraction	0	1
Spontaneous abortion	1	10
Undelivered (including 6 postmortem cesarean sections)	9	9
Dilatation and evacuation	0	10
Total	15	70

The various types of anesthesia used for delivery are shown in Table IX. Ether was used most often in the early years of the study, 1937 to 1940. Regional analgesia or anesthesia has been our method of choice during the past ten years. Although these methods were not controlled completely, we believe that low spinal or continuous caudal anesthesia lessens cardiac strain and is safer than inhalation anesthetics.

TABLE IX. TYPES OF ANESTHESIA UTILIZED IN DELIVERY OF 565 PATIENTS WITH HEART DISEASE

ANESTHESIA	NO. OF CASES
Spinal (procaine or Pontocaine)	141
Caudal	123
Nitrous oxide	88
Ether with or without nitrous oxide	168
Pentothal Sodium (D and E)	4
Cyclopropane	12
Morphine and scopolamine (alone)	5
Demerol	10
None	14
Total	565

Period 1948-1952

Results Compared With the Institution of the Cardiac-Obstetric Clinic

As stated before, a Cardiac-Obstetric Clinic for the examination and care of pregnant patients with heart disease was established in 1948. Since then examinations have been performed by the cardiologist and obstetrician at the same clinic visit and close consultation and cooperation are maintained. This close attention has materially affected our care of these patients, as shown in Tables X to XVIII.

TABLE X. ETIOLOGICAL TYPES OF HEART DISEASE AMONG 41,361 PREGNANT WOMEN, 1937-1947 AND 1948-1952, INCLUSIVE

ETIOLOGY	NO. OF CASES	
	1937-1947	1948-1952
Rheumatic heart disease	324	137
Hypertensive heart disease	51	11
Congenital heart disease	18	8
Acute bacterial endocarditis	2	0
Syphilitic heart disease	1	0
Acute pericarditis	1	0
Arteriosclerotic heart disease	1	0
Miscellaneous	11	0
Total	409	156
Total heart cases 1937-1952		565

Table X shows the relative number of patients seen during these two periods, 1937-1947, before the Cardiac-Obstetric Clinic, and 1948-1952, since the institution of the Clinic. The incidence of cardiac disease in the early group is 1.5 per cent; in the latter group (1948-1952) is 1.05 per cent.

TABLE XI. DISTRIBUTION OF PATIENTS WITH HEART DISEASE AMONG THE FOUR FUNCTIONAL CLASSES

	CLASS 1	CLASS 2	CLASS 3	CLASS 4
1937-1947.—				
Total number of cases	206	143	46	14
Number of patients digitalized	3	65	46	14
1948-1952.—				
Total number of cases	68	72	14	2
Number of patients digitalized	2	25	14	2

Table XI reveals the distribution of patients with heart disease among the four functional classes. There is some relative decrease in the number of functional classes 3 and 4 in the last five years, which may have some significance, due to the earlier treatment and prevention of decompensation.

Maternal Mortality.—

TABLE XII. MATERNAL DEATHS RESULTING FROM CARDIAC AND NONCARDIAC CAUSES

1937-1947.—	
Total number of pregnant women delivered in hospital	26,628
Total number of maternal deaths (cardiac and noncardiac)	44
Maternal mortality (all causes)	0.16%
Maternal mortality of cardiac origin (14 deaths)	0.05%
1948-1952.—	
Total number of pregnant women delivered in hospital	14,733
Total number of maternal deaths (cardiac and noncardiac)	11
Maternal mortality (all causes)	0.074%
Maternal mortality of cardiac origin (1 death)	0.006%

The maternal deaths from all causes have decreased in the past five years (1948 to 1952), there being 11 deaths in 14,733 deliveries for a percentage of seventy-four thousandths (0.074 per cent). At the same time only one pregnant patient with cardiac disease died. This patient, M. A., aged 20 years, unregistered, was admitted to the hospital on an emergency basis. She was six months pregnant and in acute cardiac decompensation. All therapeutic measures failed. Death occurred four hours after admission (Table XIV).

TABLE XIII. MATERNAL MORTALITY RATE OF PREGNANT PATIENTS WITH HEART DISEASE ACCORDING TO FUNCTIONAL CLASSES

	1937-1947	1948-1952
Total number of cases studied	409	156
Total number of deaths among cardiac patients	14	1
a. Number of deaths in functional classes 1 and 2	3	0
b. Number of deaths in functional classes 3 and 4	11	1
Maternal mortality rate in pregnant cardiac patients	3.4%	0.65%

Table XIII shows a marked decrease in the mortality rate in pregnant cardiac patients, from 3.4 per cent in 1937-1947 to 0.65 per cent in 1948-1952. This is statistically significant and shows improved cardiac and obstetric care, prenatally, at delivery, and in the puerperium.

TABLE XIV. CAUSES OF MATERNAL DEATH AMONG 565 PREGNANT WOMEN WITH HEART DISEASE

CAUSES OF MATERNAL DEATH	1937-1947	1948-1952
Acute congestive failure	5	1
Acute congestive failure with pneumonia	4	0
Acute bacterial endocarditis	2	0
Acute congestive failure and rupture of aorta	1	0
Acute exacerbation of rheumatic endocarditis	1	0
Pulmonary embolism	1	0
Total	14	1

Fetal Mortality.—

The fetal mortality shows little change in the two groups. Prematurity still remains the greatest single cause of death.

TABLE XV. CAUSES OF FETAL DEATH

	1937-1947	1948-1952
Prematurity	22	5
Undelivered (including 6 postmortem cesarean sections)	8	1
Spontaneous abortions (or D and E)	7	8
Hysterotomy	0	1
Miscellaneous	17	1
Total	54	16
Fetal mortality rate in cardiac patients	13.2%	10.2%

Types of Delivery and Anesthesia Employed.—

TABLE XVI. METHODS UTILIZED FOR DELIVERY OR TERMINATION OF PREGNANCY IN 565 PATIENTS WITH HEART DISEASE

METHOD	1937-1947	1948-1952
Low forceps	196	85
Midforceps	0	4
Spontaneous delivery	95	41
Cesarean section	74	14
Hysterotomy and evacuation	15	1
Breech extraction	9	2
Undelivered (including 6 postmortem cesareans)	8	1
Spontaneous abortions	7	3
Dilatation and evacuation	5	5
Version (second of twins)	0	1
Total	409	157
Incidence of cesarean section	18.1%	8.9%

The use of low forceps has increased in the more recent group, in line with the technique of shortening the second stage of labor at the earliest and safest time. Cesarean section incidence has decreased from 18.1 per cent in the 1937-1947 group to 8.9 per cent in the 1948-1952 group. The role of cesarean section for the patient with heart disease has become a limited one and the operation is not justified where the sole indication is heart disease. The one possible exception to this general rule is coarctation of the aorta. This condition entails certain special risks during labor, since the hypertension may lead to rupture of the ascending aorta which is often subject to developmental defects. Subarachnoid hemorrhage may also occur in this condition, from an associated congenital cerebral embolism (Benham, 1949). There is, therefore, special reason to avoid the risk of labor in this condition and cesarean section seems justified, although a normal labor and delivery may be permitted if the hypertension is slight and the obstetrical conditions are favorable.

TABLE XVII. TYPES OF ANESTHESIA UTILIZED IN THE DELIVERY OF 565 PATIENTS WITH HEART DISEASE

ANESTHESIA	1937-1947	1948-1952
Spinal	50	91
Caudal	105	18
Nitrous oxide	80	8
Ether with or without nitrous oxide	166	2
Cyclopropane	0	12
Morphine and scopolamine (alone)	5	0
Demerol (with or without scopolamine)	3	7
Pentothal Sodium (D and E)	0	4
None	0	14
Total	409	156

The incidence of regional analgesia or anesthesia has increased in the later years. These improved methods of pain relief have diminished the strain of labor and have prevented the involuntary "bearing down" pains of the terminal portion of the second stage. At the same time they have lessened the use of oxytocics in the third stage, which has frequently been mentioned as the cause of difficulties in the pregnant patient with heart disease. The convalescence of patients delivered under regional block has also been improved.

TABLE XVIII. CORRELATION OF MATERNAL AND FETAL DEATHS WITH METHOD USED TO TERMINATE PREGNANCY

METHOD	1937-1947		1948-1952	
	MATERNAL DEATHS	FETAL DEATHS	MATERNAL DEATHS	FETAL DEATHS
Low forceps	3	3	0	0
Midforceps	0	0	0	0
Spontaneous delivery	2	12	0	6
Cesarean section	0	7	0	0
Hysterotomy and evacuation	0	11	0	1
Breech extraction	0	1	0	0
Spontaneous abortion	1	7	0	3
Undelivered (including 6 postmortem cesarean sections)	8	8	1	1
Dilatation and evacuation	0	5	0	5
Total	14	54	1	16

There is no apparent correlation between the maternal and fetal deaths and the type of delivery (Table XVIII).

Special Considerations

Rheumatic Heart Disease.—

Rheumatic heart disease is the most common type seen in obstetric practice, accounting for 85 to 95 per cent of all cardiac disease in pregnant patients. In our series 461 cases of rheumatic heart disease were seen (81.6 per cent). Mitral stenosis and insufficiency are the most frequent forms of valvular lesions encountered, and occurred alone in 80.6 per cent of the patients. Next in frequency are aortic valve defects, and combined mitral and aortic disease was present in 17.2 per cent of the patients. A double valvular defect naturally imposes a greater risk. Seven deaths occurred in patients with mitral disease alone and 5 deaths in the group with combined lesions.

Congenital Heart Disease.—

Congenital forms of heart disease during pregnancy are gaining relative importance. Although the incidence of congenital malformations at this age is somewhat rare, the aggregate number is considerable. Cooley has estimated, for instance, that 20,000 women in the United States have coarctation of the aorta. This combined with other defects requires consideration in relation to pregnancy. In this series congenital defects of the heart were found in 26 patients. The anatomical lesions are shown in Table XIX.

The differential diagnosis of congenital heart disease has improved and surgical techniques are being developed that can compensate in many cases for the defects in the early stages of pregnancy, thereby lessening the risk. The

greatest risks imposed by congenital heart disease are those of congestive failure and subacute bacterial endocarditis. Antibiotic therapy has aided considerably in the treatment and prevention of severe effects of the latter. Cyanosis is an unfavorable factor in proportion to its degree and persistence. Persistent cyanosis is a contraindication to a continuation of pregnancy unless cardiac surgery can correct the condition.

TABLE XIX. TYPES OF LESIONS DIAGNOSED IN PATIENTS WITH CONGENITAL HEART DISEASE

ANATOMICAL LESION	NUMBER OF CASES
Patent ductus arteriosus	10
Intraventricular septum defect	8
Coarctation of the aorta	2
Pulmonary stenosis	4
Undiagnosed	2
Total	26

The more common abnormalities such as small auricular and ventricular septal defects are usually compatible with pregnancy, if carefully observed during this time. Patent ductus arteriosus involves the threefold danger of congestive failure, subacute bacterial endocarditis, and venous-arterial shunt. The natural termination of patent ductus arteriosus is congestive failure, and, if failure is imminent, pregnancy may precipitate it. In patients with good cardiac reserve, the prognosis is good, as the other two risks seldom materialize.

Hypertensive Heart Disease.—

This series revealed 62 patients with hypertensive cardiovascular disease complicating pregnancy. The diagnosis was based on the criteria mentioned previously, namely, a history of prolonged hypertension prior to pregnancy, and blood pressure studies for a least one week post partum, showing a systolic level of 140 mm. Hg and a diastolic level of at least 85 mm. Hg. The methods of delivery of hypertensive patients are shown in Table XX.

TABLE XX. METHODS OF TERMINATION IN 62 PATIENTS WITH HYPERTENSIVE CARDIOVASCULAR DISEASE

METHODS OF DELIVERY	NO. OF CASES
Low forceps	18
Spontaneous	16
Cesarean section	16
Hysterotomy and evacuation	8
Breech extraction	2
Dilatation and evacuation	1
Spontaneous abortion	1
Total	62

In recent years a close relationship of essential hypertension to various aspects of toxemia has been recognized, and the toxemia incidence in hypertensive pregnant patients is approximately 30 per cent. Likewise, a patient with hypertension has only about a 50 to 60 per cent chance of completing pregnancy without complications. Evidence is present, too, that hypertension may be closely related to a threat of thrombosis and infarction.

When the hypertension is severe and is complicated by cardiac enlargement, the risk is seriously increased. If pre-eclampsia occurs with hypertension, the chance of obtaining a live baby is decreased 33 per cent, and the normal risk of maternal death is increased 35 per cent.

Management

Three primary considerations must be the basis for management of heart disease in pregnancy:

I. An understanding of the physiologic changes in the circulation in the normal pregnant woman and the changes in the pregnant woman with heart disease.

II. The diagnosis and assessment of the pregnant woman with heart disease.

III. The treatment extending through pregnancy, delivery, and the puerperium.

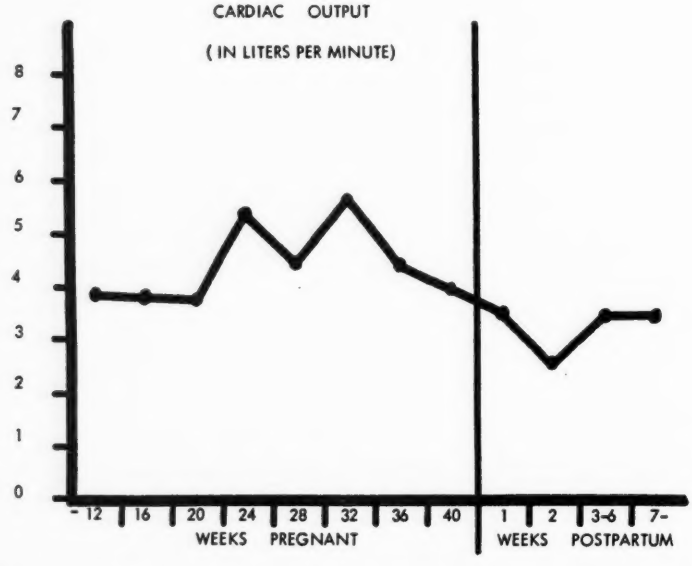

Fig. 2.—The cardiac output in pregnancy. (Figs. 2 to 9 modified from Cohen and Thomson, 1939; Clayton and Oram.)

I. Physiological Changes.—

In order to achieve a rational approach to the problems of diagnosis and supervision of heart disease in pregnant women there is involved a knowledge of the physiological changes that occur in the circulation during pregnancy. Without such knowledge the physician can neither properly appreciate the nature and extent of the additional burden that pregnancy imposes on the damaged heart, nor will he be fully aware of the several ways in which the normal circulatory changes of pregnancy can simulate organic heart disease.

1. Increased output of the heart: The most important change in the circulation during pregnancy is the increase in the heart output. Stander and Cadden (1932) and Burwell and Strayhorn (1933) have shown that, in normal gesta-

tion, the cardiac output rises above the normal level and steadily increases until, at the time of greatest output, the average increase in minute volume amounts to approximately 50 per cent above normal.

There is some difference of opinion concerning the time in pregnancy that the heart output is greatest and upon the extent of the increase. Until 1936 it was believed that this added circulatory burden steadily increased as pregnancy advanced, reaching a maximum at term. Cohen and Thompson (1936) were the first to believe the peak load of cardiac output was reached by the thirty-fourth to thirty-sixth week, and that an appreciable lightening of the cardiac burden occurred during the succeeding weeks before term and after delivery. Burwell, Strayhorn, and Flickinger confirmed these observations in 1938. Palmer and Hamilton in 1949 further verified the time of maximum output as being after the thirty-second week of pregnancy by cardiac catheterization (Fig. 2).

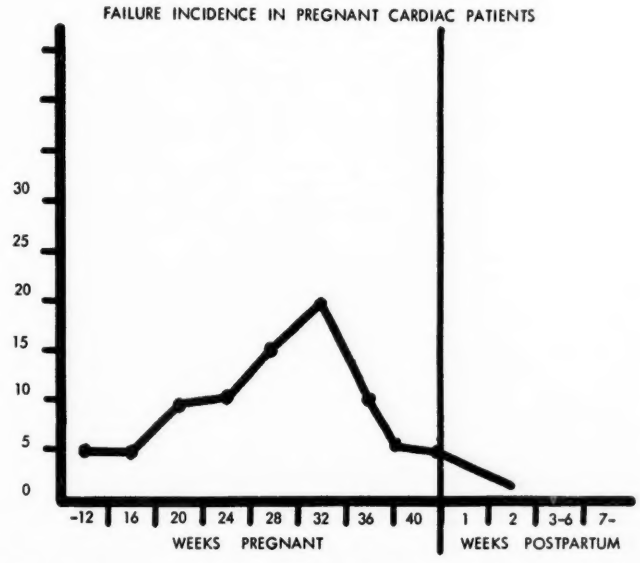

Fig. 3.—The incidence and time of heart failure in pregnant cardiac patients.

The clinical significance of this increased and decreased cardiac output becomes valuable in the management of pregnant patients with heart disease. Hamilton and Thomson (1942) showed that the incidence of failure closely parallels these increases and decreases in heart output. Heart failure steadily increased in pregnancy up to the thirty-second week, and primary failure seldom occurs after that time (Fig. 3).

The work of Hamilton and Thompson was instrumental in discouraging the dangerous practice of inducing premature labor by medical or surgical means.

2. Increased blood volume and plasma: Increased blood volume and plasma closely parallel the increase and decrease of the heart output during pregnancy. These two factors are probably closely related and with the similarity of the incidence of heart failure occurring with the rise and fall of the output and

volume, it seems reasonable to direct treatment toward lowering the output and blood volume. The blood volume increase reaches a maximum of about 45 per cent, which is due almost entirely to the increased plasma volume (Fig. 4).

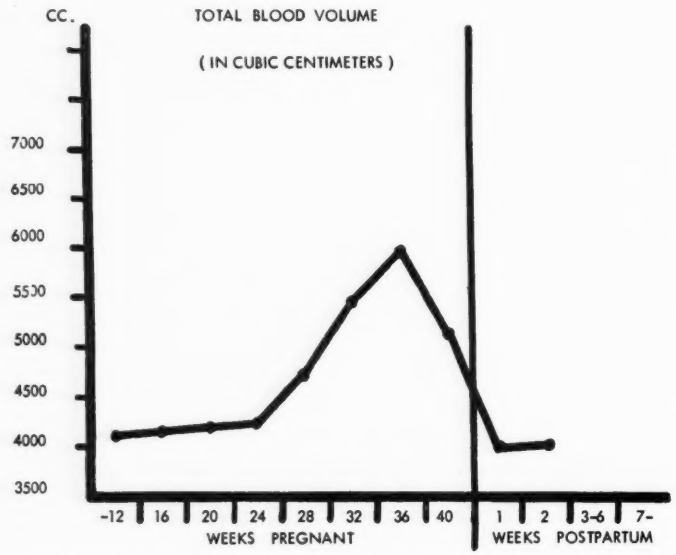

Fig. 4.—The total blood volume changes in pregnancy. The maximum increase is around the thirty-second to the thirty-fourth week.

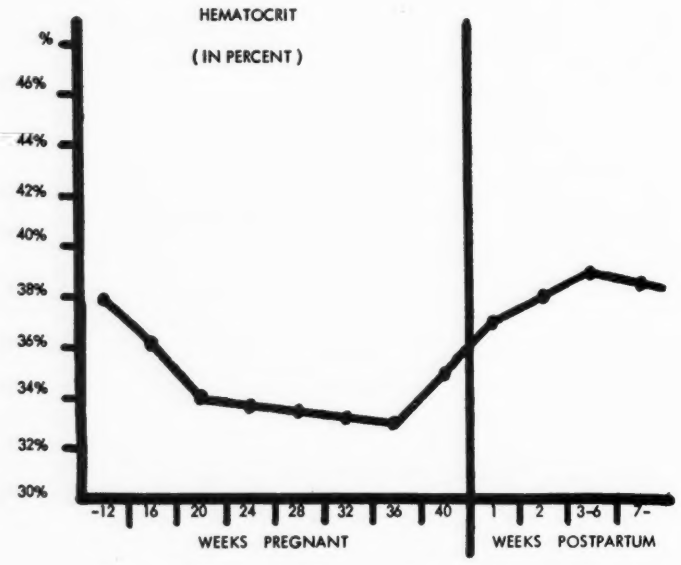

Fig. 5.—Changes in the hematocrit during pregnancy.

Confirmation of this increase was made by Cohen and Thomson (1936), who made hematocrit studies during pregnancy and found that progressive blood dilution occurs, reaching a maximum after the thirty-second week and then retrogresses similar to the heart output and blood volume (Fig. 5).

The blood viscosity shows a relative lowering as the volume increases (Fig. 6).

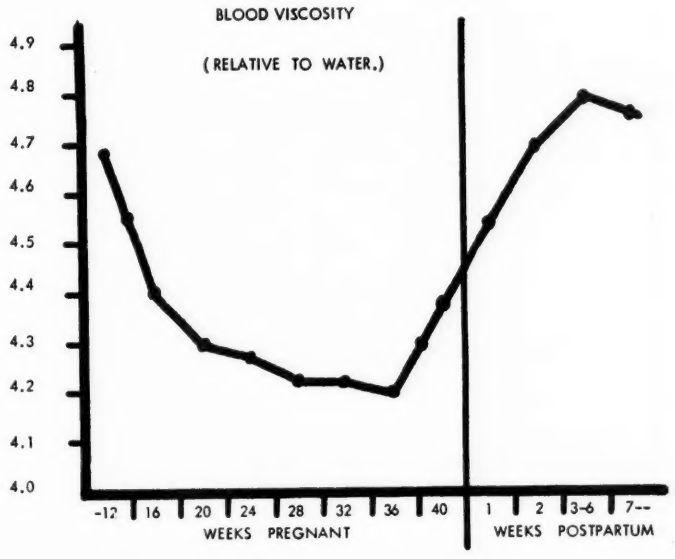

Fig. 6.—The blood viscosity in pregnancy shows a relative lowering as the volume increases.

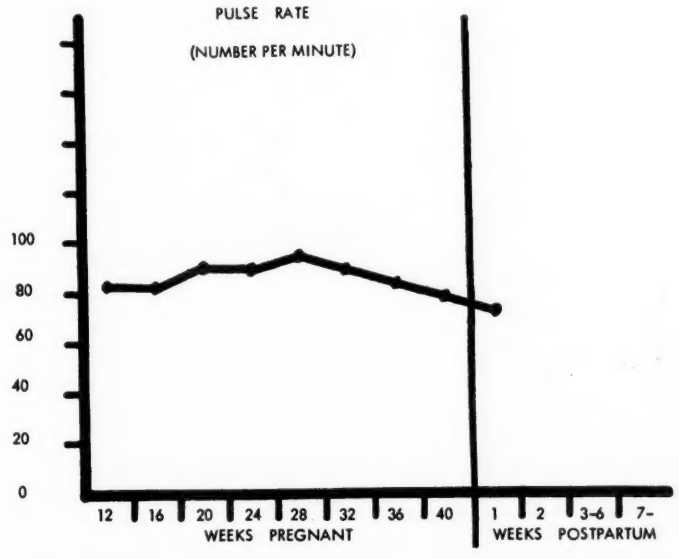

Fig. 7.—The heart rate changes in pregnancy. It accelerates gradually up to the thirtieth week and then diminishes to term.

The increased cardiac output can be attained by either an increase in the stroke volume of the heart, in the heart rate, or both. As the increase in stroke volume is less than the increase in minute volume, there must be an increase in the heart rate in pregnancy (Fig. 7). This accelerates gradually up to the thirtieth week and gradually decreases from then on to the delivery.

3. Changes in blood pressure, pulse, and venous pressure: The blood pressure shows gradual changes in the systolic and diastolic readings to shortly before delivery and then a lowering to below normal in the puerperium (Fig. 8).

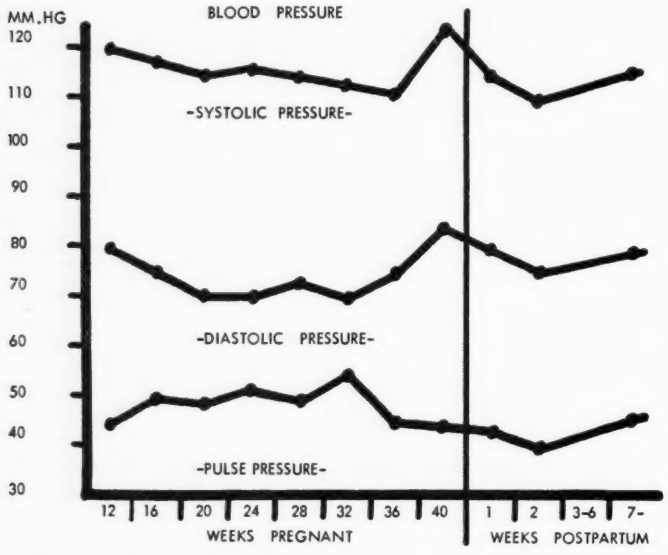

Fig. 8.—The systolic, diastolic and pulse pressures in pregnancy.

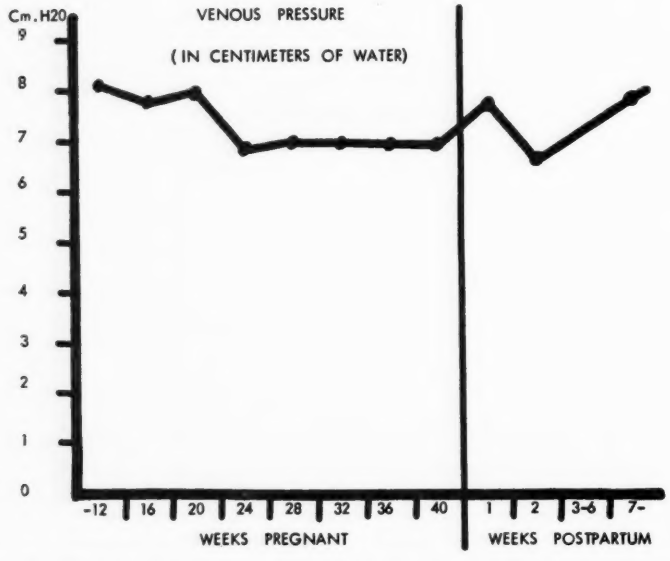

Fig. 9.—The venous pressure of the upper extremities during pregnancy.

The pulse pressure shows relative changes. It diminishes before the onset of labor.

The venous pressure of the upper extremities in pregnancy without heart disease shows a slight decrease in the first two trimesters of pregnancy and

remains below normal until after delivery (Fig. 9). In pregnancy with heart disease venous pressure varies little unless signs of failure appear, at which time it rises.

4. Increase in vital capacity and oxygen consumption: Thomson and Cohen in 1938 showed that the vital capacity has a distinct tendency to increase slightly, due to an increase in the transverse diameter of the chest. This increase may reach as much as some 12 per cent over the average normal nonpregnant value. Likewise, the values of oxygen consumption rise slightly in pregnancy, reaching a maximum shortly before delivery, and return to normal immediately within the first week of the puerperium (Fig. 10).

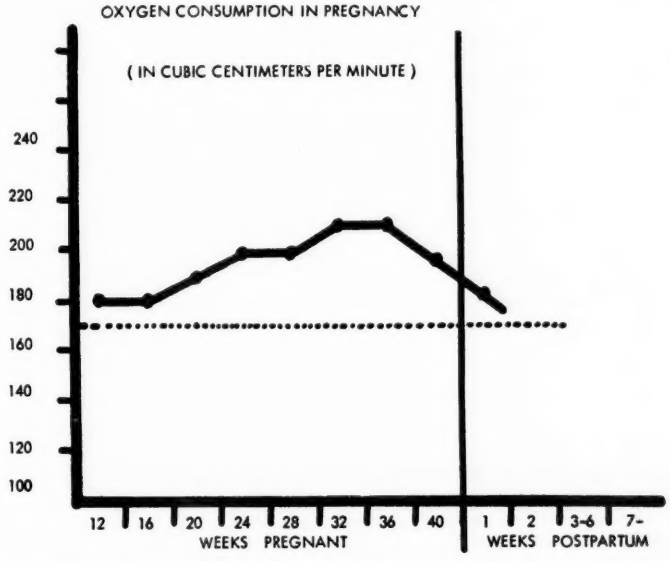

Fig. 10.—The consumption of oxygen rises slightly in pregnancy, reaching a maximum shortly before term. (Modified from Jones, A. M., 1951.)

5. Retention of fluid: Extracellular fluid volume follows closely the increase in plasma volume throughout pregnancy. Water retention in the blood and tissues occurs during pregnancy and the positive salt balance during gestation was shown by Chesley in 1944, with the loss of large quantities of salt during the puerperium. Crabtree (1939) indicated that there is considerable salt retention during pregnancy and accounts for the water retention in the blood and tissues. The importance of salt retention in patients with heart disease was first emphasized by the work of Warren and Steed in 1944, who showed patients with severe heart disease confined to bed, the free administration of salt producing congestive failure, which then could be relieved by restricting the salt intake. They believed that retention of water and salt is the initial step in the development of heart failure and precedes the rise of venous pressure. They attributed this excretory failure to decreased renal flow. Merrill in 1946 supported this view. This is of great importance to us in that it is of value in the pathogenesis and prevention of heart failure during pregnancy when there is so pronounced

a tendency to salt and water retention. Gillam (1949) in a preliminary study found the plasma volume could be lowered with the restriction of salt in pregnancy complicated by heart disease (Fig. 11).

Other alterations of physiology may also affect the increased load of pregnancy. The normal weight gain in pregnancy of 20 to 22 pounds may add increased tissue demands for circulation. Strain on the trunk musculature produced by a change in the center of gravity may add increased burden on the circulation. Certain fetal factors likewise may affect the cardiovascular load of pregnancy. The gravid uterus is rich in vascularity and the arteriovenous placental communications may act as fistulas and impose continuous amplified cardiac work.

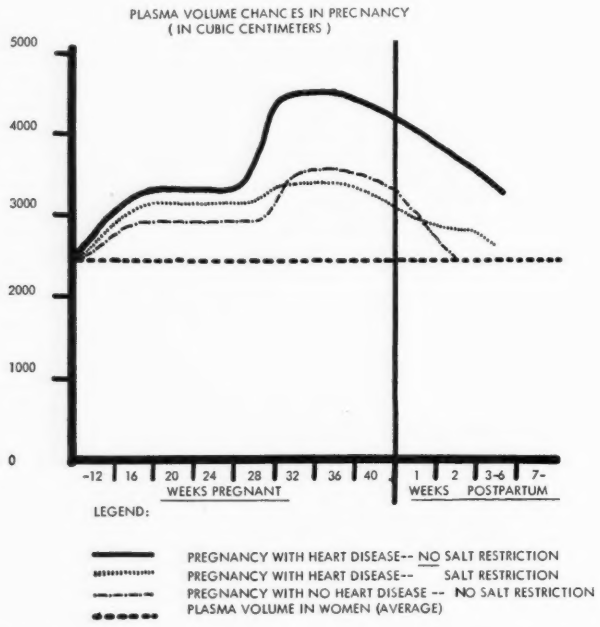

Fig. 11.—The plasma volume changes in pregnancy, with and without complicating heart disease, in relation to salt intake and restriction.

In summary, then, the important physiological changes that occur in pregnancy in the normal patient indicate that when a patient with heart disease becomes pregnant three factors increase the liability of failure: (1) increase of heart output; (2) increase in blood volume; and (3) retention of salt and water. These three changes appear to be intimately bound together during pregnancy, when all reach their maximum at approximately 34 weeks of pregnancy and then decline on through term and the puerperium. Consequently, the safe and successful management of pregnancy in heart disease must be directed toward an attempt to reduce the incidence of failure in patients by preventing excessive salt and water retention. Thus the changes in water balance and in blood volume which may be to some extent controlled are of great practical importance to us in our consideration of heart disease occurring during pregnancy.

II. Diagnosis and Assessment of the Patient With Heart Disease in Pregnancy.—

With the knowledge of the physiological changes that occur in normal pregnancy, the management of the patient with heart disease in pregnancy is dependent upon the diagnosis and assessment of the individual patient. It is in this field that the cardiologist can be of greatest value to the obstetrician in helping to evaluate the extent and severity of the heart lesion in pregnancy. We have seen how pregnancy increases the work of the heart and how the gravid uterus places an abnormal strain, possibly one of serious moment, on the damaged heart. It therefore becomes conceivable that under the changing conditions of pregnancy overtaxing of a damaged heart may produce irreversible change and precipitate failure. Since 1948 we have maintained our cardiac clinic for pregnant patients in the same room as the prenatal clinic. Here the cardiologist examines the patient at the same visit that the obstetrician evaluates her from the obstetric viewpoint. At this time the symptoms of the patient are carefully evaluated by both and a detailed analysis is made, in close cooperation, of the weight changes, blood pressure, pulse, diet, urinalysis, dyspnea, and the complete physical examination.

This method expedites the cardiac diagnosis and coordinates the medical and obstetrical management of patients. Any patient suspected of a cardiovascular abnormality is referred for evaluation. Many are found to have only a functional murmur associated with pregnancy, but those patients who have organic heart disease are followed jointly through prenatal care, delivery, and the follow-up examinations. Special provision is made for Social Service follow-up on all cardiac patients. Any absence from prenatal appointments immediately alerts the outpatient staff. A home visit is made to the patient and she is hospitalized if ill.

In the assessment of the patient, the history of rheumatic fever is important. By far the larger percentage of patients will recall having the disease in childhood if it has occurred. The history of previous heart failure is important, as another failure may be anticipated with the added burdens of pregnancy. On the other hand, if a previous pregnancy was not complicated by failure, it should never be assumed that it cannot occur at this time. The parity of the patient is of doubtful significance in itself, but increased parity is associated with increased age, which may be a factor.

The cardiovascular symptoms and signs of pregnancy must be carefully evaluated, as certain ones may be common to both the normal pregnant woman and the cardiac patient. It is essential that their origin be recognized to avoid errors in diagnosis and to avoid unjustifiably labeling a patient with "heart disease."

1. Dyspnea: Dyspnea on exertion frequently occurs in the normal pregnant patient, especially in the last trimester, and is due to increased total ventilation in excess of the more modest rise in vital capacity. Nocturnal dyspnea and orthopnea may occur due to the diminished respiratory reserve.

2. Pain: The left submammary pain of effort syndrome is common in pregnancy. It is aching or stabbing in character and frequently localized to the palpable cardiac impulse. It may radiate through the chest to the left scapular region or to the left shoulder and arm. Such pain usually occurs when the patient is tired or at rest and often disappears when she is working or occupied. It is unlikely to be confused with anginal pain which is constantly related to exertion, is constricting in character, and more often starts in the midline.

3. Palpitation: Cardiac palpitation frequently occurs during or immediately after exertion, and is usually due to an overactive heart. Heart consciousness may be noticed, especially during the night, accompanied by a choking sensation. This can be differentiated from the nocturnal dyspnea of heart failure with its wheezing respirations, cough, and frothy or blood-tinged sputum.

4. Heart and pulse rate: On examination of the pregnant woman, irregular pulse due to premature beats or sinus arrhythmia is found. Mild tachycardia (10 to 20 beats per minute) frequently is present, with a loud first sound in the mitral area, causing the hyperkinetic syndrome of Harrison (1935). It should not be misinterpreted as real tachycardia.

5. Murmurs: Murmurs are frequently present in pregnant women. Pulmonic systolic murmurs are almost constant findings. The second pulmonic sound may be accentuated. Mitral systolic murmurs are commonly heard, but diastolic murmurs are not attributable to pregnancy and should never be considered functional. The murmurs heard are usually blowing in character, localized, and vary with alterations in posture and breathing. Triple rhythm is another peculiarity heard in pregnancy which disappears after delivery. It is usually due to the increased cardiac output. It should not be confused with a congenital heart lesion.

6. Edema: Uterine enlargement tends to increase venous pressure in the pelvis and lower extremities. Edema produced by this means is observed frequently during pregnancy. However, if there is evidence of increased venous pressure in the upper extremities, as evidenced by prominence of cervical veins, the presence of congestive heart failure is strongly suspected. The edema of pregnancy must be carefully evaluated, too, from the standpoint of weight increase, salt retention, and beginning renal failure with toxemia.

7. Enlargement of liver: The liver is never palpable below the costal margin in normal pregnancy. When it is, it points to congestive heart failure.

8. Râles: Persistent or posttussive râles are *not* due to normal pregnancy.

9. Cardioscopy or fluoroscopy: This reveals an increase in both the longitudinal and transverse diameters of the heart. With the ascent of the diaphragm, the heart comes to lie transversely and has a more flattened appearance, closely resembling that due to mitral stenosis.

10. Electrocardiography: Left axis deviation (15 degrees) occurs in pregnancy. A large Q_3 may become evident as pregnancy advances, and T_3 may become inverted. This has no special portent, and a knowledge of these changes occurring during pregnancy is insurance against a misdiagnosis of coronary artery disease.

Functional Classification.—One of the most difficult problems in assessment of cardiac pregnant patients is to decide which ones present serious therapeutic problems and which will require no more than ordinary supervision. No scientific or satisfactory method exists for measuring cardiac reserve in a patient. Therefore, we find the functional classification of the New York Heart Association most helpful in estimating the cardiac risk, beginning with the first trimester of pregnancy.

The classification:

Class 1.—Patients with cardiac disease and no limitation of physical activity

Class 2.—Patients with cardiac disease and slight limitation of physical activity

Class 3.—Patients with cardiac disease and marked limitation of physical activity

Class 4.—Patients with cardiac disease who are unable to carry on any physical activity without discomfort

Although this classification is of great value in assessing the functional status of the cardic pregnant patient, it does not answer all the problems of determining how the patient will respond during pregnancy. Such factors as the age of the patient, size of the heart, the duration of the disease, history of previous failure, disturbance of rhythm, the structural lesions of the heart, evidence of rheumatic activity, and the presence of concomitant disease—all should be considered and evaluated by the cardiologist and the obstetrician.

Procedure for Handling of the Pregnant Patient With Heart Disease.—Although every case *must be handled on its own individual merits* and exceptions may occur whenever an attempt is made to classify treatment, the majority may have certain procedures recommended (Table XXI).

III. Treatment.—

A. Antepartum treatment:

1. Prenatal visits to Obstetric-Cardiac Clinic
2. Rest
3. Diet: high protein; low salt and fluid intake in second and third trimesters
4. Avoidance of infections
5. Vitamin intake
6. Control and treatment of anemia
7. Digitalis therapy
8. Termination of pregnancy
9. Cardiac surgery

The most gratifying management of pregnancy complicated by heart disease can be attained only by integrated cooperation of the obstetrician and internist-cardiologist. The Division of Obstetrics and Gynecology of the Pennsylvania Hospital has enjoyed this cooperation during the sixteen years of this

TABLE XXI. SUGGESTED PROCEDURES

FUNCTIONAL CLASSIFICATION	CARDIAC PATIENT NOT PREGNANT	CARDIAC PATIENT PREGNANT	
Class 1	May advise patient there is no unusual danger in pregnancy	*First pregnancy:* Normal pregnancy under supervision of cardiologist and obstetrician	*Subsequent pregnancies:* If no signs of failure another pregnancy carries no additional risk after full convalescence
Class 2	Advisability of pregnancy depends on: 1. Ability to have prenatal care 2. Circumstances of patient	*First pregnancy:* a. Normal pregnancy under supervision of cardiologist and obstetrician b. Hospitalization before delivery c. Second stage shortened by low forceps	*Subsequent pregnancies:* If no permanent heart damage nor signs of failure, another pregnancy permissible after convalescence
Class 3	Pregnancy inadvisable	Early in pregnancy: termination considered Late in pregnancy: safest to allow to continue to term; usually vaginal delivery; short second stage	Pregnancy inadvisable
	Possibility of cardiac surgery in selected patients		
Class 4	Pregnancy inadvisable	Early in pregnancy: termination considered Late in pregnancy: prognosis grave; safest to allow vaginal delivery; short second stage	Pregnancy inadvisable
	Possibility of cardiac surgery in selected patients		

study. It has been particularly close since the adoption of one Clinic for both specialists to see the cardiac-obstetric patient at the same time. We believe it has had a profound effect on the reduction of maternal mortality. Only one maternal cardiac death has occurred in the past five years since the inception of this Clinic.

The advice and attention given in these Clinics have been the responsible factors. Examinations are carried out at frequent intervals throughout pregnancy, usually one or two weeks, depending upon the patient's physical condition and functional classification. Signs of congestive heart failure are carefully watched for—râles at the bases of the lungs, edema, or palpable liver enlargement, in addition to cough, hemoptysis, cyanosis, increased weight gain, or increased venous pressure.

Advice is given to the patient concerning the maximum rest possible. At least one to two hours in bed every afternoon and ten to twelve hours nightly are recommended.

The diet prescribed for the patient is liberal with special attention to a normal weight gain in pregnancy of 20 to 22 pounds. Efforts are made to watch this detail closely, as we believe essential nutrition is a vital factor in the prevention of complicating toxemia of the patient and prematurity of the infant.

The increased extracellular fluid volume during pregnancy naturally predisposes to edema, but, as Gillam has shown in his preliminary studies, plasma and blood volume can be reduced with limitation of salt during the second and third trimesters. This tends to prevent edema and with limitation of fluid lightens the burden of the heart in the pregnant cardiac patient. An ordinary diet contains 6 to 15 Gm. of salt per day (Wheeler, quoted by Gillam, 1947). This can be reduced to 3 to 4 Gm. if no salt is added at the table or in cooking, and to 1.5 Gm. if salt-free bread and butter are used. Possibly cation exchange resins may allow liberalization of salt intake under certain conditions.

It is impressed upon the patient that the appearance of any unusual symptoms is reason to report to the physician at once. Upper respiratory infection or dental infection is sometimes a precipitating factor of acute congestive failure. Seven of our fatalities, which occurred in the early years of this study (1937-1943), were due to infection. None has occurred since the close attention of the Clinic to infections and to the early, judicious use of antibiotic therapy.

The intake of vitamins B_1 and C should be several times the minimum daily requirement and we advise supplementation with additional vitamins and minerals in the form of polyvitamin-mineral capsules daily.

The control of anemia during pregnancy is especially important to the cardiac-obstetric patient, and an iron preparation is freely used. The response to the iron deficiency anemia is usually good with molybdenized iron. Sometimes this must be augmented by saccharated iron intravenously, or small (200 to 300 c.c.) repeated whole blood transfusions. Care and caution should be exercised not to overload the circulation of the cardiac pregnant patient and only small transfusions should be given. Some clinics advocate packed red blood cell transfusions. We have not used this method.

It is unnecessary to describe the details of digitalis administration, as this properly resides in the hands of the cardiologist. It is accepted that digitalis therapy is valuable in congestive failure, and should be instituted at once if the earliest signs appear, whether due to either right- or left-sided failure. Once digitalis therapy has been instituted during pregnancy, it is usually advisable to continue a maintenance dose at least until after delivery.

The question of termination of pregnancy may arise. This should be left largely to the cardiologist who emphasizes that termination should never be done until the cardiac condition has been adequately treated. Interference is rarely justified except, perhaps, in early pregnancy.

The advent of improved techniques in cardiac surgery offers a new outlook in certain selected cardiac pregnant patients, and reports in the literature of surgery performed during pregnancy are increasing. Mitral commissurotomy has been performed during pregnancy by Brock, Rumel, Cooley, and others, with uneventful, successful delivery at term. Apparently there is no reason to fear mitral valvular commissurotomy during pregnancy provided the orthodox indications for the procedure are present. With the decreased mortality experience, this operation may save the lives of pregnant-cardiac patients previously despaired of, and allow the continuation of pregnancy to term.

Increasing numbers of patients have undergone commissurotomy, later have become pregnant, and then have been delivered at term without event (Bailey). This may change the outlook and prognosis in many women with cardiac disease who wish to become pregnant, but have been advised against it.

Other lesions, such as coarctation of the aorta, septal defects, pulmonary or aortic stenosis, are being treated successfully by surgery. Patients with these lesions may be cured of their cardiac disease and later they may become pregnant and deliver without difficulty.

B. Intrapartum treatment:

1. Hospitalization
2. Cardiologist present at delivery
3. Sedation
4. Methods of delivery
   a. Vaginal, short second stage, forceps and episiotomy (elevation of head)
   b. Cesarean section, only for obstetrical indications, except possibly coarctation of the aorta
5. Analgesia and Anesthesia
   a. Regional
      1. Spinal
      2. Caudal
      3. Pudendal
   b. General
      1. Nitrous oxide
      2. Cyclopropane
      3. Ether—obsolete
6. Avoidance of oxytocics in the third stage of labor
7. Observation of the patient
8. Treatment of acute failure during labor or delivery
   a. Elevation of head—high Fowler position
   b. Continuous caudal analgesia
   c. Phlebotomy
   d. Oxygen
   e. Digitalis
   f. Short second stage
   g. No oxytocics

The management of labor and delivery is principally a matter for the obstetrician but we seek the close cooperation of our cardiologist and he is present whenever the cardiac condition may cause anxiety. The resident cardiologist of the hospital is informed immediately upon admission of the cardiac-obstetric patient to the hospital, and the cardiac status is re-evaluated by him, while the obstetrician checks the obstetric condition. In functional Classes 3 and 4 patients are admitted at least one week before term for observation, rest, and stabilization. Digitalization is not done on all patients, only when indicated.

With the onset of labor, sedation is administered early to prevent undue fatigue and anxiety. We believe barbiturates are contraindicated. Ample nutrition is maintained with fruit juices by mouth. Frequent blood pressure, pulse, and respiration rate records are made, at least each half hour or more often, if indicated. Any signs of impending congestive failure, such as rapid pulse and respiration, or basal râles, are carefully watched.

The progress of labor is followed closely, as early termination is desirable when the cervix is completely dilated and the position and presentation are favorable. This prevents undue stress and strain and avoids the use of the voluntary and involuntary efforts at this time. Mature obstetrical judgment is obligatory.

We prefer and advocate the use of regional or conduction block analgesia, such as low single injection spinal, or continuous caudal infiltration. Evidences of our increasing use of these techniques can be seen by the employment of these methods in only 37 per cent of the cases in the first group (1937-1947) and the increase to 70 per cent in the second group (1948-1952). The methods are safe when their techniques are thoroughly known and properly executed.

The development of pulmonary edema from acute congestive failure following delivery makes the third stage of labor a very critical period. It is due to overfilling of the lesser circulation with blood returning in great quantities from the uterine sinuses when the uterus has contracted. Oxytocics increase the contractility of the uterus and thus may throw additional strain on the heart and pulmonary circulation. We do not advise the use of oxytocics in the cardiac patient for this reason, unless the postpartum loss of blood is great and they are necessary for the control of hemorrhage.

The patient is carefully observed following delivery, and she is not moved from the delivery room for at least one hour. The pulse, blood pressure, and respirations are observed frequently during this time.

Should acute congestive failure occur in labor, delivery, or immediately after delivery, measures must be instituted quickly. The head of the bed must be raised to the orthopneic position at once. Intravenous digitalization is rapidly initiated. The failure is usually right sided in nature, but may be of either or both sides of the heart. Phlebotomy has a definite place in our treatment and should be done when necessary. The institution of continuous caudal analgesia has the same effect as phlebotomy, and may be used to relieve right-sided failure. Its action is to cause peripheral vascular dilatation in the lower extremities and thus relieve the heart and pulmonary edema. Oxygen administered continuously to the patient during this time is of value. The second stage of labor should be shortened as mentioned above and oxytocics withheld after delivery. All of these measures must be used quickly and expertly to avoid maternal death.

C. Postpartum treatment:

1. Rest and avoidance of infection
2. Early ambulation only for patients in Classes 1 and 2

3. Digitalis therapy
4. Nursing of baby
5. Home care
6. Follow-up examination
7. Prognosis for future pregnancies
8. Intercourse
9. Sterilization

The dangers of puerperal infection are increased in the patient with heart disease. It is desirable to keep her in the best possible state of nutrition. Food is allowed on the regular house diet if she shows no untoward effects of the delivery. Vitamin and iron supplement is maintained. There is risk of organisms settling on the damaged heart valves, and subacute bacterial endocarditis has been a cause of death in the past. We have favored the use of chemotherapy or antibiotic therapy if any suggestion of infection is present and have on occasions given the medication prophylactically.

In patients whose hearts have decompensated—those in Groups 3 and 4—two-hour pulse and blood pressure charts are kept for the first five days after delivery. Sedatives should be given to ensure restful sleep and avoidance of worry. Early ambulation is practical only in patients in Classes 1 and 2 if no signs of failure have appeared. Patients in Classes 3 and 4 are kept in bed for a varying number of days depending upon the severity of the heart disease.

Where digitalis therapy has been used before delivery the practice is to continue a maintenance dosage for some weeks following delivery. Here again, the length of time is dependent upon the lesions present.

Lactation, or the nursing of the baby, seems to increase the circulatory demands, although this is not clearly established. Our practice has been to advise against nursing if a significant cardiac lesion is present. It can prove to be a hazardous risk for patients in functional Classes 3 and 4. Winfeld (1930) found that lactation prevented the metabolism of the patient from returning to normal until six weeks after delivery. It should be avoided if there is any reason for the mother to conserve her strength.

The burden of childbearing is not confined to the prenatal period, labor, and delivery of the child. This is particularly meaningful for the patient with heart disease. It may be many months before recuperation is complete. During this period it is important to control the activity of the patient in her home. Ample rest should be maintained, and if the care of her child and home together makes this impossible, some steps must be taken to provide assistance for her. Our Social Service worker from the Cardiac-Obstetric Clinic is often able to provide the necessary aid.

The follow-up examination is usually made six weeks after delivery. At this time the patient is examined by both the cardiologist and obstetrician. If her health is good she is then referred to the regular Cardiac Clinic for heart care and to the Gynecologic Clinic for further care.

The problem of another pregnancy should be discussed with every patient during the postpartum visit, as this is the time she is most concerned and usually

the most receptive to advice. This opportunity must not be neglected, as there is a possibility of the clinic or physician not seeing the patient again until she is again pregnant. Full recuperation time is not likely to be under twelve months, and another pregnancy should not be started within twelve to eighteen months following delivery. One must caution against too long a delay, too, for the heart disease will not improve after this time, and may even progress in severity. Further, the age of the patient increases, and, as Eastman (1944) has stated, greater obstetrical difficulties may be encountered. Careful observation in the cardiac clinic may help to answer this problem.

Advice as to contraception may be given if compatible with religious principles. It may be essential if we are to advise these patients most helpfully. Mackenzie (1921) has expressed such clear views on the problem of intercourse in cardiac patients, that I can do no more than quote them: "The domestic happiness of married couples is often marred by the injudicious advice of doctors, who have, on account of fears of the hearts of patients, forbidden intercourse. I know of no heart condition which should act as a deterrent, when the woman feels competent. . . . If she experiences afterward nothing but a passive exhaustion, there is no ground for objection, however affected her heart may be."

If another pregnancy is absolutely inadvisable, then sterilization is perhaps the only certain method of preventing conception. A total of 47 sterilizations were performed in the 565 patients who were under our care. The hypertensive cardiovascular group had the largest number of tubal ligations done. The method used was usually the Pomeroy technique with ligation and sectioning of the Fallopian tubes. Sterilization was performed in 21 patients at the time of cesarean section, and in the remaining ones in the puerperium. We do not advise sterilization if there is a possibility that pregnancy may be undertaken again with reasonable safety.

Summary

In a review of the histories of 41,361 women delivered at the Pennsylvania Hospital during the years 1937 to 1952, inclusive, the total number with heart disease was found to be 565, an incidence of 1.12 per cent.

The maternal mortality rate in the pregnant cardiac patient was 2.6 per cent (15 maternal deaths). The fetal mortality rate was 12.3 per cent (70 fetal deaths). Heart disease has occupied the most prominent position as a cause of maternity mortality, accounting for 27.2 per cent of the maternal deaths from all causes during the sixteen years reviewed in our hospital.

Acute congestive failure was the cause of death in 11 of the 15 deaths. Infection was the precipitating factor in 7 cases. Prematurity was the leading cause of death in the babies.

The pregnant cardiac patients were divided into two groups: those delivered from 1937 to 1947, and those delivered from 1948 to 1952. The purpose was to analyze the groups in relation to the establishment of the Cardiac-Obstetric Clinic in 1948. Only one maternal death from heart disease has occurred since its inception, that of an unregistered patient.

From the analysis of our patients, we believe the problems of management of pregnancy with heart disease should include the following:

1. An understanding of the physiological changes in the circulation in the normal pregnant woman and the changes in the pregnant woman with heart disease
2. The diagnosis and assessment of the pregnant woman with heart disease
3. Proper and adequate treatment during pregnancy, delivery, and puerperium

The different phases of treatment are discussed in detail. Certain techniques in treatment, such as the increased use of forceps for delivery, conduction block anesthesia, and use of digitalis therapy are emphasized.

Close cooperation between the cardiologist and the obstetrician at all times is strongly advocated.

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Discussion

DR. ROBERT A. JOHNSTON, Houston, Texas.—The study of 565 cases of heart disease occurring in approximately 41,000 deliveries gives a true picture of the problem in Philadelphia and offers to us in other sections of the country helpful suggestions in combating this major problem, especially since there has been such a marked reduction of maternal deaths from hemorrhage, infection, and toxemia.

It has long been my clinical impression, and this concept also has been shared by several internists whom I have interrogated, that rheumatic heart disease is not as frequently encountered in the Southwest as along the Eastern Seaboard, in Colorado, or in Mexico City. A review of approximately 8,500 obstetrical records in two Houston hospitals during the past year revealed only 15 cases in which cardiac disease of rheumatic origin was complicated by pregnancy. One death occurred in this small series. I feel certain that this low incidence of cardiac disease is incorrect and, if more careful histories had been recorded and more painstaking examinations of the patients had been made, the incidence of the disease would have been much larger. No doubt, Dr. Ullery's presentation will stimulate many of us to investigate this problem as it affects our local communities.

As our attention is called to the physiology of pregnancy, no one can greatly disagree with the author that the thirty-second to the thirty-fourth week of pregnancy is the critical period because of the increase of heart output, increase in blood volume and plasma, and the retention of salt and water, but can one offer a satisfactory reason or

explanation as to why it takes place at such a time rather than later? However, this knowledge has resulted in benefit to the patient because the physician refrains from any interference at this particular time.

The selection of the type of anesthesia is a controversial issue in obstetrics, varying as one travels to different sections of the country. Even in the same city one finds advocates of regional anesthesia in one hospital, intelligent opposition to it in another. No doubt each advocate is sincere in his feeling in regard to the virtues and inadequacies of general or regional anesthesia. Dr. Ullery has, however, offered strong factual evidence supporting the use of regional anesthesia. On the other hand, the cardiac surgeons extol the safety and stability of action of ether. Is it not probable that the planned stabilization of all cardiac symptoms under the expert guidance of a cardiologist, the use of the technical wizardry of a well-trained anesthetist familiar with all types of anesthesia, working in conjunction with the obstetrician—all these combined factors offer such safety that the forces of nature are allowed to perform their function of childbirth successfully? This may be the explanation for the decreased incidence of cesarean sections performed in this study.

With the astounding success which has accompanied heart surgery in cases of congenital as well as acquired abnormalities, the obstetrician will be confronted from time to time with new problems. In 110 cases of cardiac surgery, performed by Denton Cooley in Houston, there were 5 pregnant women. In each case the results for both mother and baby were excellent. Experimental studies on pregnant dogs in different stages of pregnancy are being undertaken to ascertain if marked lowering of the body temperature has any detrimental effect on the puppies in utero. If this procedure is found innocuous, further studies can be made in heart surgery.

Each obstetrician may profit by the wise counseling and the judicious advice in the management of heart disease complicated by pregnancy presented by this interesting study.

DR. JOHN F. CUNNINGHAM, Dublin, Ireland.—The most important factor in the management of pregnancy in the cardiac patient is early diagnosis. If the existence of a cardiac lesion is diagnosed while the heart is still in a reasonably good functional condition, a successful result for both mother and infant may be anticipated. This diagnosis is not always easy and is not infrequently missed.

In Ireland some 90 per cent of cardiac disease in pregnant women is rheumatic in origin. While a history of rheumatic fever, chorea, etc., in childhood or adolescence, is helpful in attracting attention to the possibility of the presence of a cardiac lesion, such history is obtainable in only about 50 per cent of cases. An account of the exercise tolerance of the patient, before pregnancy, is often helpful.

Routine examination of the heart should be carried out at the patient's first visit. In the early months of pregnancy and especially about the third month, systolic murmurs, splitting of the first or second sound, or various irregularities may be present. These are frequently functional in origin, are often associated with some degree of anemia and are largely attributable to the physiological changes occurring at this time. As pregnancy advances these abnormal findings usually disappear. In the presence of true cardiac disease, on the other hand, the heart may appear normal at first examination and it may require a second or third examination to demonstrate the existence of a genuine lesion. If any doubt exists as to the diagnosis, a cardiologist should be consulted.

Time does not permit me to refer extensively to the literature on this subject nor to pay tribute where it is due. I will, therefore, limit this communication to the methods of treatment and the results obtained at the National Maternity Hospital, Dublin, a hospital with which I have the honor to be long associated. This hospital deals with some 5,000 deliveries annually, including many nonbooked and emergency admissions. The cases which I will quote have been directly under the care of the present Master, Dr. A. P. Barry and his team, with Dr. M. Drury, J. Murray-Hayden, and Philip Brennan, Consultant Cardiologists.

In assessing the degree of cardiac debility, I follow the functional classification recommended by the New York Heart Association. Success in treatment is dependent on adequate rest, avoidance of infections, prevention of anemia, restricted fluid and sodium intake, and noninterference with the pregnancy. The patient in Class 1 may be treated as ambulatory, provided that she restricts her activity and reports for examination at frequent intervals. The patient in Class 2 may be treated at home, but must have twelve hours' rest per day. This may be divided into ten hours at night and two in the early afternoon. The patient in Class 3 or 4, or any patient who has recently had decompensation or auricular fibrillation, is admitted to hospital and detained until after delivery. In all cases, the intake of sodium is drastically restricted and the fluid intake and output controlled. The diet may also be restricted if the increase in weight is too great. Anemia is prevented or treated in the usual way. Infections of any kind are dangerous, especially those of the respiratory tract, and should receive immediate and serious attention. The patient receiving home treatment (Classes 1 and 2) is admitted to hospital about the thirty-seventh week and kept at rest in bed until delivery. Sufficient doses of digitalis are given, depending on the response and tolerance shown.

Interference with the pregnancy is undesirable and unnecessary and may lead to dangerous complications. In almost all cases the onset of spontaneous labor should be awaited. If signs of decompensation develop during pregnancy, digitalis and mercurial

TABLE I. SUMMARY OF TREATMENT AND RESULTS IN 310 CONSECUTIVE CASES OF RHEUMATIC CARDITIS

CASES	LESION		METHOD OF DELIVERY		MORTALITY	CHILD		
						STILLBORN	NEONATAL DEATH	ABORTION
Class 1.—								
138 patients	Mitral	132	Forceps	16				
	Mitral and aortic	5	Breech	5	Nil	3	2	5
Average age, 30.6 years	Aortic	1	Cesarean section (threatened rupture)	1				
Average parity, 3.03			Spontaneous	116				
Class 2.—								
94 patients	Mitral	87	Forceps	11				
	Mitral and aortic	5	Breech	3	Nil	2	1	2
Average age, 32.6 years	Aortic	2	Cesarean section (placenta previa)	1				
Average parity, 4.1			Spontaneous	79				
Class 3.—								
45 patients	Mitral	37	Forceps	7				
	Mitral and aortic	8	Breech	1	Nil	2	4	–
Average age, 31.8 years	Aortic	–	Cesarean section (repeat)	1				
Average parity, 4.7			Spontaneous	36				
Class 4.—								
33 patients	Mitral	26	Forceps	6				
	Mitral and aortic	7	Breech	1	2	3	1	1
Average age, 32.9 years	Aortic	–	Cesarean section (repeat)	1				
Average parity, 4.3			Laparotomy	1				
			Spontaneous	25				
Total 310					2	10	8	8

diuretics are helpful. More advanced signs, such as pulmonary edema, are relieved by continuous oxygen and, if necessary, by venesection. Aminophyllin (0.25 Gm. intravenously) is also helpful. To induce labor or to empty the uterus surgically, during or approximate to an attack of decompensation, is too dangerous to be contemplated.

Cardiac disease, of itself, is not an indication for delivery by cesarean section, but an added complication may call for such surgical intervention. Induction of premature labor is unnecessary, since the cardiac burden lessens after the thirty-second week. If hydramnios is present it is treated in the usual manner.

During the first stage of labor, sedatives such as morphine, Dilaudid, or pethidine (Demerol) may be used. The patient is confined to bed and is usually most comfortable in a semirecumbent position. Any evidence of cyanosis should be treated by the administration of oxygen, in the interests of both mother and fetus. Should the pulse and respiration rates increase, oxygen, sedatives, digitalis, and venesection should be employed. If, now, labor is still likely to last for some time, intervention is often necessary. The alternative rests between cesarean section and incision of the cervix and forceps extraction. The choice of method will be dependent on the conditions present and the easier method should be used.

The second stage should not be allowed to impose too much strain on the heart and straining efforts by the patient should be avoided. Multiparas will usually deliver themselves but many primigravidas will need assistance by forceps. In either case episiotomy will facilitate delivery.

A word about anesthesia. Local infiltration is safest in any method of delivery. Sodium thiopentone may be used by a skilled anesthetist with the aid of a suitable apparatus for the administration of oxygen. Cyclopropane depresses cardiac action and is not recommended. Ether is not desirable owing to its tendency to produce chest complications.

The patient still requires careful observation during the early days of the puerperium. Any elevation of temperature is treated immediately, owing to the danger of subacute bacterial endocarditis.

The table gives details of 310 consecutive cases of rheumatic carditis treated at the National Maternity Hospital during the last four years. It does not include cases in which the cardiac lesion was due to other causes, comprising about 10 per cent of the gross total, but none of these cases gave rise to anxiety or to a fatal termination.

Of the two maternal deaths, one was due to a virus pneumonia at 34 weeks which did not respond to treatment; the second was due to a quiet rupture of a classical scar with a twin pregnancy at 34 weeks, emergency admission, laparotomy, adherent bowel also found torn, death from peritonitis.

In no case was abortion or labor induced, and no patient was sterilized.

Of the four cesarean sections, one was done for rupture of the uterus; one was for placenta previa, and two were repeat sections, one having disproportion. These were the only four in the series.

DR. DUNCAN E. REID, Boston, Mass.—I am sure we are in general agreement with the medical and obstetric management of heart disease in pregnancy as outlined by Dr. Ullery. He has conclusively demonstrated that the maternal mortality from heart disease may be reduced to an extremely low figure when obstetric and cardiac care are integrated. In a large maternity service this is best achieved through the efforts of a special clinic whose only function is the care of the cardiac patient.

I thought it might be of interest to this association to review some of the experience in our community with patients in whom cardiac surgery was performed during pregnancy or who had a pregnancy after cardiac surgery. Because of the high incidence of rheumatic heart disease in New England, we at the Boston Lying-in Hospital have had an opportunity to observe a rather large number of pregnant women with cardiac disability. Before commenting further, I should like to state that our clinic holds the view that a certain small percentage of cardiac patients should not attempt pregnancy or, if seen early in

gestation, continue their pregnancy. These so-called "unfavorable" cardiac patients approximate 5 per cent of all of our patients with heart disease. The most important single criterion for placing patients in this group is previous cardiac failure.

The patients in our hospital who have benefited most from cardiac surgery include younger individuals with severe mitral stenosis and patients with coarctation of the aorta. The former group oftentimes develop heart failure in the form of paroxysmal dyspnea. These attacks of acute pulmonary edema may appear initially and perhaps only during pregnancy. These individuals presumably have a very tight mitral valve with resultant severe pulmonary hypertension. Because of the small mitral opening these patients are unable to cope with the enlarged blood volume of pregnancy, and bouts of paroxysmal dyspnea may result. Relief of the pulmonary hypertension through enlargement of the mitral orifice (valvuloplasty) obviates cardiac failure in these patients, or at least postpones it for many years. We have in times past terminated the pregnancy in such patients and taken steps to eliminate the hazards of future pregnancy. Recent advances in cardiac surgery have challenged such a policy and we have had to modify our views, particularly in the younger and less parous group of women. Undoubtedly, the number of cardiac patients with an unfavorable prognosis seen in pregnancy will be reduced by cardiac surgery, but the frequency remains to be determined.

When acute pulmonary edema appears suddenly without any previous signs of heart failure in pregnancy, the enthusiastic cardiac surgeon may wish to operate immediately on the patient. Whether the pregnancy should be first terminated and cardiac surgery performed subsequently remains controversial. The preparation of the patient for cardiac surgery involves the elimination in so far as possible of all burdens on the circulation. Pregnancy is considered a burden to the damaged heart. At our hospital, we favor termination of the pregnancy, to be followed some time later by the appropriate cardiac surgery. If in the mind of the cardiologist the therapeutic response is satisfactory, the patient may subsequently undertake another pregnancy.

Our cardiologists are familiar with a series of eight patients in and about our community who had valvuloplasties for severe mitral stenosis during pregnancy. There was one postoperative death. Six of the patients did well and the pregnancies were successful. One patient proved to have mitral insufficiency rather than stenosis at the time of operation. She subsequently became a patient at the Boston Lying-in Hospital, showing evidence of rather severe cardiac failure. After the necessary medical preparation the pregnancy was terminated at the fourth month and the patient recovered and was discharged, improved. Even an expert cardiologist with all the newer diagnostic techniques may erroneously conclude that the patient has predominantly a mitral stenosis rather than cardiac insufficiency. The therapeutic response in the latter presumably would be nil, and in the case of the pregnant patient the added trauma of cardiac exploration might be disastrous.

In addition, two patients have been delivered successfully on the house service at the Boston Lying-in following valvuloplasty performed prior to pregnancy. Their cardiac disability has been markedly less since correction of the mitral stenosis, and neither had recurrent failure in pregnancy. Fourteen similar cases in which the patients have had relatively normal pregnancies after mitral valve surgery have been collected and reported by our Medical Group at the Boston Lying-in Hospital (Burwell, C. Sidney, and Ramsey, L. H.: Surgery of the Mitral Valve and the Management of Mitral Stenosis in Pregnant Women, Tr. A. Am. Physicians [In press]).

The final group about which opinion differs with respect to the advisability of pregnancy is made up of patients with coarctation of the aorta. We have had three patients who have had resections of the aorta for coarctation and who have subsequently had a pregnancy. In all, the hypertension was significantly improved. Dr. Ullery suggests that cesarean section might be indicated for the delivery of these patients. All we can say is that these three patients had uneventful pregnancies and were delivered normally.

DR. J. P. GREENHILL, Chicago, Ill.—I am sure that most of you were impressed by the first chart, which showed the causes of death at the Pennsylvania Hospital. I was

surprised to see that hemorrhage ranked third, not first, in the list of causes of maternal death. The most frequent cause of death was cardiac disease. In the United States as a whole, as well as in most large cities individually, infection has been overcome to such a degree that it no longer holds first place in maternal mortality. Hemorrhage is now the primary cause of maternal mortality, but not at the Pennsylvania Hospital. This undoubtedly is due to the excellent type of obstetrics done there, because as you noticed on the chart there has not been a death from hemorrhage in the last several years.

The matter of anesthesia in cardiac cases is very important. On one of the slides three types of regional anesthesia were mentioned—caudal, spinal, and pudendal. I believe that at the Pennsylvania Hospital no patients with cardiac disease were delivered under direct infiltration anesthesia which, as mentioned by Dr. Cunningham, is the safest of all forms of anesthesia.

There were 104 laparotomies, of which 88 were cesarean sections, and the rest were for the termination of pregnancy. Dr. Ullery, I am sure, will agree that during the last few years cardiac disease has been less and less an indication for therapeutic abortion, just as pulmonary tuberculosis and other diseases are now rare reasons for interrupting gestation. In fact, the trend has been decidedly away from therapeutic abortion for most illnesses which 15 or 20 years ago were common indications for termination af pregnancy.

One other point is this: I noticed on one of the slides that six babies died when attempts were made to save them after the death of the mother. I should like to know whether any babies at all were saved by postmortem cesarean section and, if so, whether the babies were normal. We all know that in many cases of fatal cardiac disease the patients are cyanotic for a long period of time before death. In some instances, at least, the babies show signs and symptoms of the prolonged cyanosis when born alive. Therefore I should like to ask whether any of the babies delivered postmortem were born alive and, if so, whether they remained in good health.

DR. NICKOLAS C. LOUROS, Athens, Greece.—On the occasion of this discussion I may perhaps report on a very rare case which I had a short time ago. It was that of a woman in the third month of pregnancy, presenting an enormous echinococcus cyst inside the pericardium. Signs of pressure were present and even the electrocardiogram was affected. After much discussion, operation was performed successfully, and she was delivered five months later per vaginam without any complication at all.

DR. ULLERY (Closing).—In a discussion of analgesia we do not wish in any way to be dogmatic about its use. The team of the anesthetist and the cardiologist and the obstetrician has worked together so well in our institution that we have come to look upon regional analgesia favorably in the past ten years. We feel that it has certain advantages when the technique is thoroughly understood and executed. We believe it has great value in the prevention of anoxia in the premature child, that we so often deal with in our cases of cardiac disease.

In answer to Dr. Greenhill's two questions: In the termination of pregnancy there were 16 abdominal hysterotomies. Fifteen of these occurred in the first group, from 1937 to 1947, but only one has been performed in the last five years. This shows very well, I believe, our attitude toward abortion and hysterotomy in the pregnant cardiac patient today. We feel that termination is seldom if ever necessary except in a very rare case perhaps, in the early weeks of pregnancy. There were no babies saved in our postmortem cesarean sections; all six died. As Dr. Greenhill has emphasized, the anoxia of the patients at the time of death contributed to the fetal deaths. The postmortem cesarean sections were done at the earliest possible moment that they could be performed, and even though the patients had received oxygen during the terminal phases, it did not influence the anoxia enough to save any of our postmortem babies.

LATE URINARY SYSTEM COMPLICATIONS FOLLOWING RADICAL HYSTERECTOMY FOR CARCINOMA OF THE CERVIX*

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(From the Department of Obstetrics and Gynecology, School of Medicine, University of Virginia)

URINARY system complications which are incompatible with life are common complications of untreated carcinoma of the cervix as recently emphasized by necropsy studies of Henriksen.[1] This study[1] and others[2, 3, 12] have pointed out the urological complications and the importance of urological follow-up studies in those patients with carcinoma of the cervix treated by irradiation therapy. With the revival of the surgical approach to the problem of cervical malignancy, urinary system complications remain one of the hazards of treatment with resultant urinary fistulas and their sequelae as reported by Meigs[4] and Thomas and associates.[5]

This study is a report of late urological complications in a small group of patients with carcinoma of the cervix treated by radical operation. It is the purpose of this study to present the various types of postoperative urinary system complications as seen in our clinic.

Material

The study consists of 33 patients treated by radical surgery from April, 1948, to May, 1953. The group of patients is small and constitutes approximately 9 per cent of the total number of new patients with cervical cancer seen during this period. The group is highly selective and consists, in general, of young patients in excellent physical condition with Stage I or early Stage II (International Classification) lesions. The youngest patient was 24 years of age and the oldest 55 years of age, with the average for the group 36 years. The types of malignancy are shown in Table I.

Table I. Types of Malignancy

Epidermoid	30
Adenocarcinoma	1
Epidermoid and adenocarcinoma	1
Adenocarcinoma and intraepithelial	1
Total	33 patients

Pregnancy was associated with the cervical malignancy in 5 patients, and 4 of these cases have previously been reported from this clinic.[6] Of the remaining 28 patients, there were 3 patients with carcinoma of the cervical stump.

Preoperative x-ray therapy as an adjunct to radical surgery was employed in the early years of the study and 12 patients received this combined type of treatment. The surgical pathological findings and x-ray dosages are shown in

*Presented at the Sixty-fourth Annual Meeting of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons, Hot Springs, Va., Sept. 10, 11, and 12, 1953.

Table II. Radical hysterectomy with radical pelvic lymphadenectomy was carried out in all patients in this group with the exception of K. C. in whom lymphadenectomy was not considered feasible. One patient, V. C., with lymph node metastases died within five months after operation and the other patient with lymph node involvement is alive and well four years after operation.

Adequate radium and x-ray therapy was given to 4 patients, in addition to those shown in Table II, who were considered to have irradiation-resistant tumors on the basis of positive biopsy for tumor after completion of therapy. These patients were then treated by radical hysterectomy and pelvic lymph node dissection. Multiple nodes contained viable tumor in 2 patients, and in the remaining 2 patients the tumor was confined to the uterus. One of the patients with lymph node involvement is living with known aortic lymph node metastases and the other patient with lymph node metastases died eight months after operation. The two patients without lymph node involvement are living and well four years after operation.

TABLE II. SURGICAL PATHOLOGY IN IRRADIATED PATIENTS

PATIENT	STAGE	AIR ROENTGENS	RESIDUAL TUMOR	NODES
F. A.	I	9,600	Vaginal wall	Negative
C. R.	I	10,400	Cervix	Negative
P. R.	I	12,000	None	Negative
H. H.	I	9,600	None	Negative
C. B.	II	8,800	Cervix, right ovary	Negative
L. W.	II	12,800	Cervix, vagina	Negative
J. Mc.	I	10,400	Cervix	Negative
K. C.	I	8,000	None	Not obtained
V. C.	I	10,000	Cervix	Multiple nodes
G. P.	I	11,200	None	Negative
M. D.	II	12,000	Cervix	Negative
C. W.	I	9,000	Cervix	Multiple nodes

Radical surgery was the only form of treatment received by 17 of the group of 33 patients. The surgical pathological findings are shown in Table III. Pregnancy was associated with the cervical malignancy in the 2 patients with lymph node involvement. One of these patients died on the seventh postoperative day of pulmonary embolism, and the second patient died 27 months after operation for cervical cancer of widespread metastatic adenocarcinoma of the breast. Necropsy examination revealed no tumor in the pelvis and all metastatic tumor was considered to be mammary in origin. Lymph node dissection was not done in 3 patients who had previously undergone pelvic surgery with resultant extensive adhesions.

TABLE III. LYMPH NODE INVOLVEMENT

Free of tumor	12 patients
Positive for tumor	2 patients
Nodes not obtained	3 patients
Total	17 patients

Preoperative Preparation

All patients in the group, with the exception of 2 patients who were in labor, had cystoscopic and intravenous or retrograde pyelographic studies prior to operation. Ureteral catheters were in place during operation in all patients, with the exception of one, in whom it was not possible to insert a ureteral catheter on the right side due to a bifid system. Thirteen patients received penicillin or penicillin and streptomycin preoperatively.

All patients received blood transfusion during the operation with an average of 2,130 c.c. of whole blood for each patient. Postoperative antibiotic therapy was given as shown in Table IV. Patients with a temperature elevation to 100° F. were considered to be febrile and the average febrile period for the 29 patients in Table IV was 9.5 days.

TABLE IV. POSTOPERATIVE ANTIBIOTICS

ANTIBIOTICS	PATIENTS	FEBRILE	AFEBRILE
Penicillin and streptomycin	27	24	3
None	6	5	1
Total	33	29	4

Operative Complications

There were no ureteral, bladder, or bowel injuries at the time of operation. The only operative death occurred several hours after completion of the operation as a result of hemorrhage. Autopsy was not permitted and it is believed that the postoperative hemorrhage was due to a ligature slipping off the uterine artery. This death and the 4 previously mentioned account for the 5 non-surviving patients in the series.

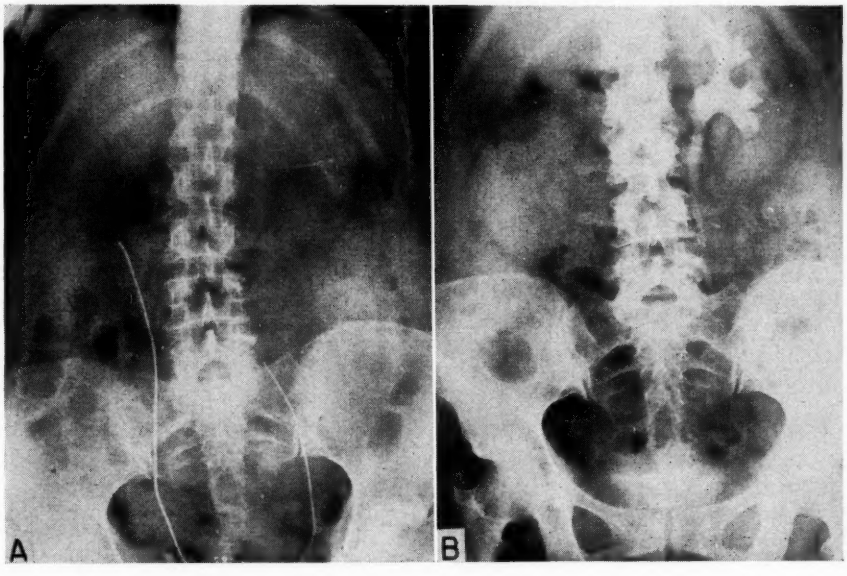

Fig. 1.—*A*, Preoperative flat plate with catheters up. Normal intravenous pyelograms at this time.

B, Twelve weeks after operation at which time ureterovaginal fistula on right had spontaneously closed. Shadow of right kidney seen, but absence of excretion of opaque material on this side. The right ureter could not be catheterized beyond the 3 cm. level. Preoperative x-ray therapy received by this patient.

Early Postoperative Bladder Complications.—

Foley catheters were maintained in the bladder in all patients on an average of 8.5 days. Following removal of the catheter in 30 patients it required on an average 19 days for each patient to empty her bladder with a catheterized residual of 60 c.c. or less of urine. The patient who died on the operative day

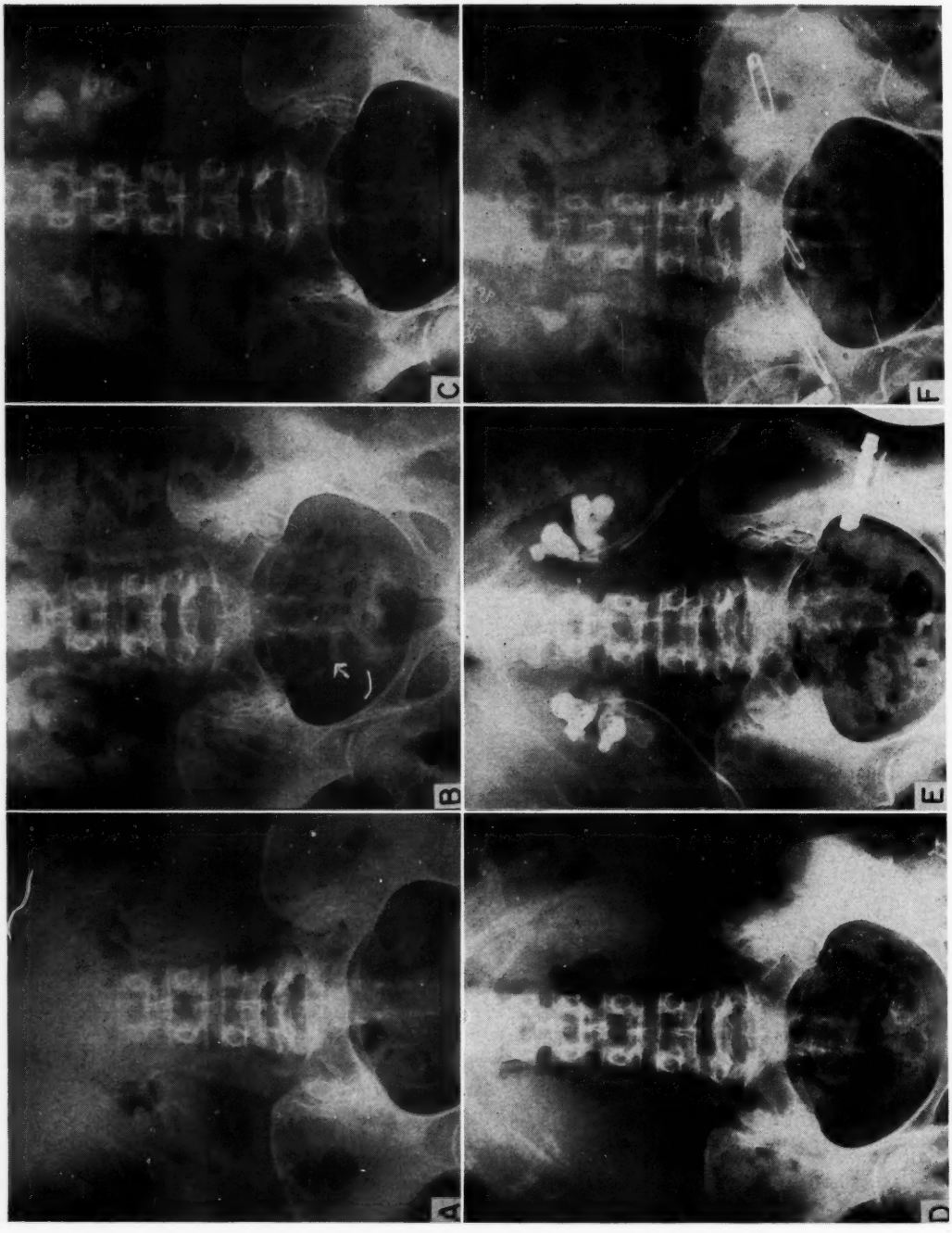

Fig. 2.—*(For legend see opposite page.)*

and the patient who died on the seventh postoperative day are not included. A third patient was unable to void for eight months at which time bilateral cutaneous ureterostomies were done for a progressing bilateral hydronephrosis.

Urinary tract infections were troublesome in spite of postoperative penicillin and streptomycin therapy, as shown in Table V. The colon group of organisms were cultured from the urine in 14 patients and in 5 patients the organism was not specified.

TABLE V. URINARY TRACT INFECTIONS

ANTIBIOTICS	PATIENTS	PYURIA	NO PYURIA
Penicillin and streptomycin	27	14	13
None	6	5	1
Total	33	19	14

There were no postoperative vesicovaginal fistulas in the series and there has not been a late vesicovaginal fistula in any of the 28 patients who survive.

Early Ureteral Injury.—

One patient developed a ureterovaginal fistula on the eighteenth postoperative day and another patient developed a ureterovaginal fistula on the forty-ninth postoperative day. Both fistulas healed spontaneously and Fig. 1 and Fig. 2 reveal the ultimate outcome in each patient.

Late Ureteral Complications.—

Of the 28 patients followed to date, 6 patients have developed upper urinary tract complications in addition to the fistulas previously mentioned. Unfortunately, one cannot assume an attitude of complacency should he be so fortunate as not to have a patient develop a ureteral fistula. In none of these patients do we suspect or identify residual tumor. Two of the 3 patients with a

TABLE VI. LATE URETERAL COMPLICATIONS

	PATIENTS	X-RAY
Nonfunctioning kidney	3	2
Nonfunctioning kidney and hydronephrosis	1	1
Unilateral hydronephrosis	1	0
Bilateral hydronephrosis	1	0
Normal pyelograms	16	8
No follow-up	6	3
Total	28	14

nonfunctioning kidney received preoperative x-ray therapy. The patient with a nonfunctioning kidney and a contralateral hydronephrosis received preoperative x-ray therapy. Roentgen therapy was not a factor in either the patient

Fig. 2.—*A*, Fifteen-minute intravenous pyelogram done prior to operation.

B, Forty-five minute study 3 weeks after operation showing dilatation of both ureters and renal pelves. Arrow marks probable fistulous tract on right.

C, Forty-minute intravenous pyelogram taken 3 months after *B*. Delayed excretion with progressive dilatation of calyces. Ureterovaginal fistula had healed spontaneously and both ureters could be catheterized to kidney levels.

D, Intravenous pyelograms after 90 minutes with kidney shadows only. Nitrogen retention of 102 mg. per cent eight months after operation.

E, Bilateral cutaneous ureterostomies with opaque catheters and retrograde injection of opaque material.

F, Intravenous pyelograms, after 25 minutes, done 18 months after ureterostomies, showing some decrease in hydronephrosis. No nitrogen retention. This patient received no irradiation therapy.

with the unilateral hydronephrosis or the patient with the bilateral hydronephrosis. The most striking observation has been the asymptomatic character of these upper urinary system complications. It is also noteworthy that these developments may occur many months after operation as shown in Figs. 3, 4, and 5.

Late Bladder Complications.—

Two of the most troublesome late developments in the 28 surviving patients have been urinary incontinence and loss of bladder sensation. Most patients

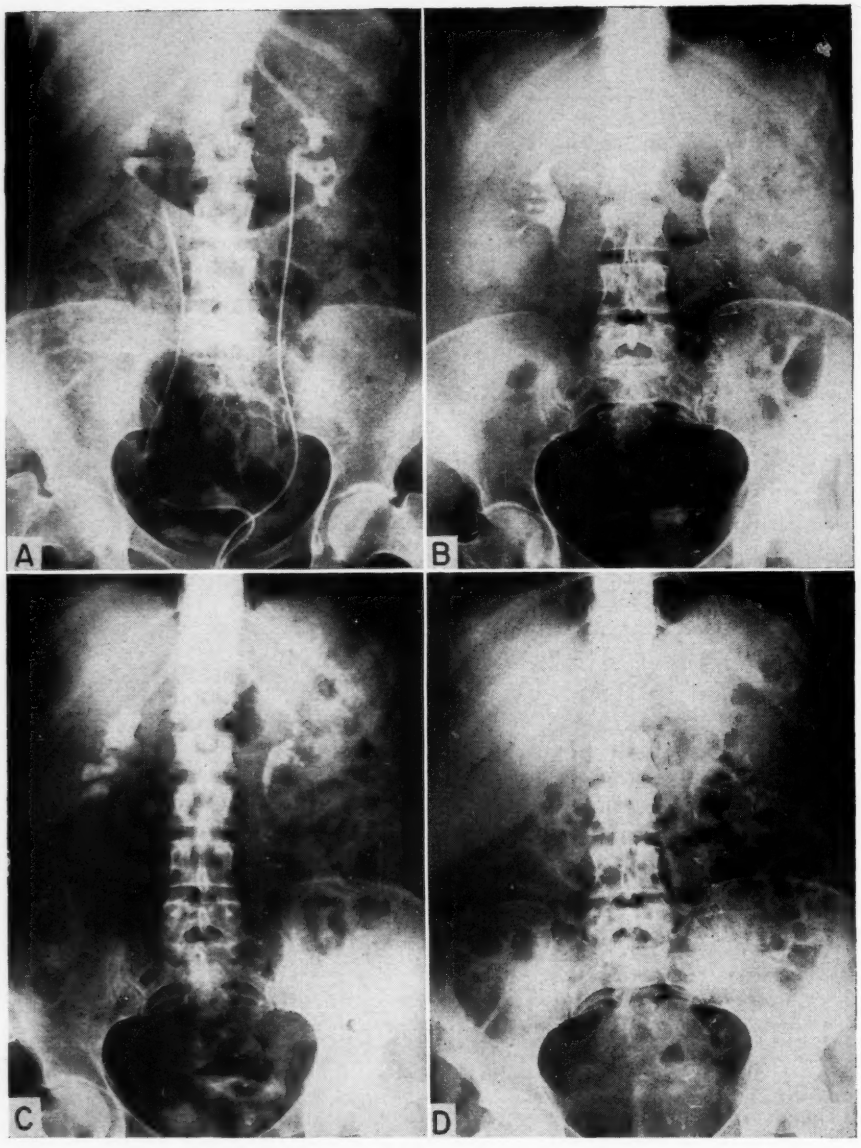

Fig. 3.—*A,* Normal retrograde studies prior to operation.

B, Five-minute intravenous pyelograms done 9 months after operation and considered normal.

C, Fifteen-minute intravenous pyelograms with hydronephrosis on the right, fifteen months after operation and no upper urinary tract symptoms.

D, Opaque material not excreted on right after 70 minutes. Normal system on left. Unable to catheterize ureter on right. Thirty months after operation. This patient treated by operation only.

experience some loss of bladder sensation for several weeks after radical hysterectomy but recover sensation and are symptom free. Twombly[7] has called attention to these complications following radical hysterectomy and has pointed out in some detail the neurological injury responsible for these problems in the operative treatment of carcinoma of the cervix.

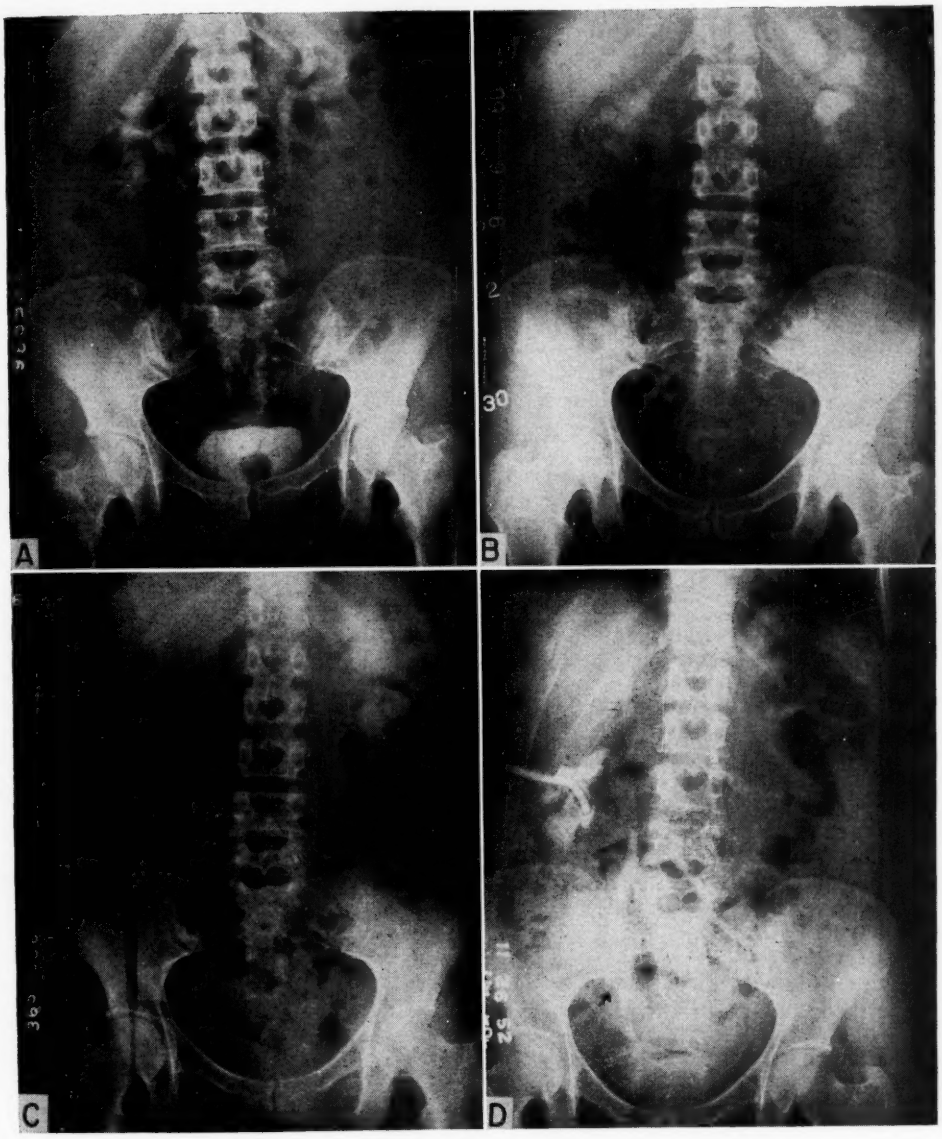

Fig. 4.—*A*, Intravenous pyelograms one month after operation showing some dilatation of right ureter and blunting of calyces. Mild dilatation on left.

B, Intravenous pyelograms done twelve months after operation. Bilateral hydronephrosis with no opaque medium in bladder after 30 minutes. Right ureter catheterized with ease. Left side showed some constriction at ureteral orifice, but No. 5 catheter could be passed with ease.

C, Three years after operation pyelogram shows marked hydronephrosis on left and after 70 minutes there was not sufficient concentration of opaque material excreted to permit visualization. Blood urea at this time was 66 mg. per cent.

D, Injection of nephrostomy tube shows dilated system with obstruction at pelvic brim. Blood urea levels returned to normal after nephrostomy. This patient received preoperative x-ray therapy.

Fifteen of the 28 patients do not have bladder symptoms and have been followed for intervals, as shown in Table VII, without difficulties. Cystometrograms in Fig. 6 graphically demonstrated recovery of function in a patient. However, the hypotonicity of the bladder does not always indicate disturbance of function. Cystometrogram (Fig. 7) done twelve months after operation shows a hypotonic bladder without disturbance of function.

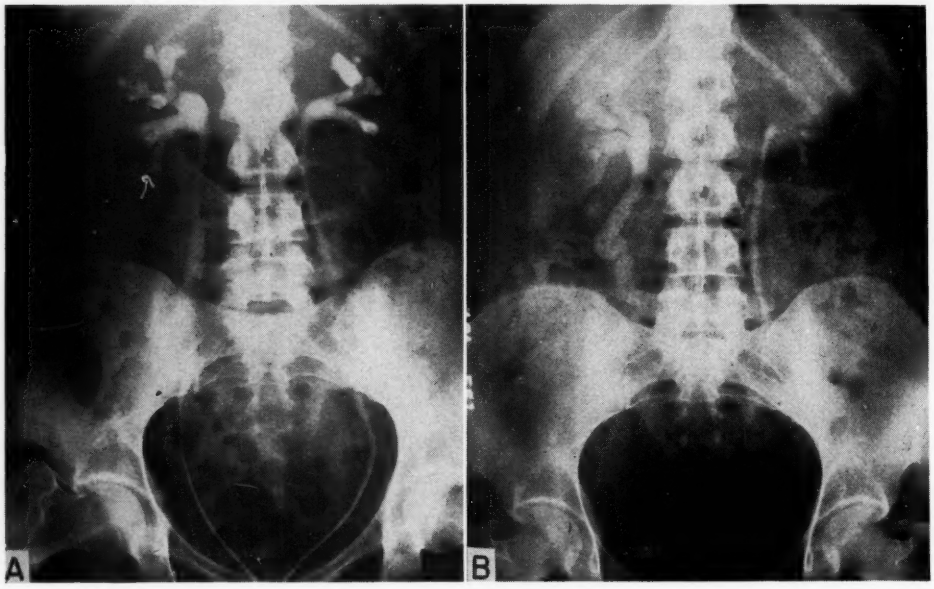

Fig. 5.—*A*, Preoperative retrograde pyelograms showing a moderate hydronephrosis on the right.

B, Twelve months after operation showing progressive hydronephrosis on 25 minute intravenous pyelography. This patient did not receive irradiation therapy.

Thirteen of the surviving 28 patients experienced more than the expected bladder difficulties and some of these patients have remained problems of management for as long as four years after radical operation as shown in Table VIII. One patient (Fig. 6) was unable to void for 75 days following operation in spite of tidal drainage and parasympathomimetic drugs. Serial cystometrograms in this patient showed progressive recovery of function and she is now asymptomatic three years after operation. The other patient with urinary retention was unable to void for eight months after operation at which time cutaneous ureterostomies were done as previously mentioned. The opportunity to explore the pelvis was afforded when the ureterostomies were done. Each ureter was found surrounded by dense scar tissue which extended from the pelvic brim to the bladder. Since x-ray therapy was not received by this patient it is concluded that infection of the retroperitoneal tissues resulted in the fibrosis and bilateral ureteral obstruction.

Two of the 13 patients had no loss of sphincter control but had severe bedwetting problems. One of these patients had a contracted bladder with a capacity of 200 c.c. with complete loss of sensation on forceful distention of the

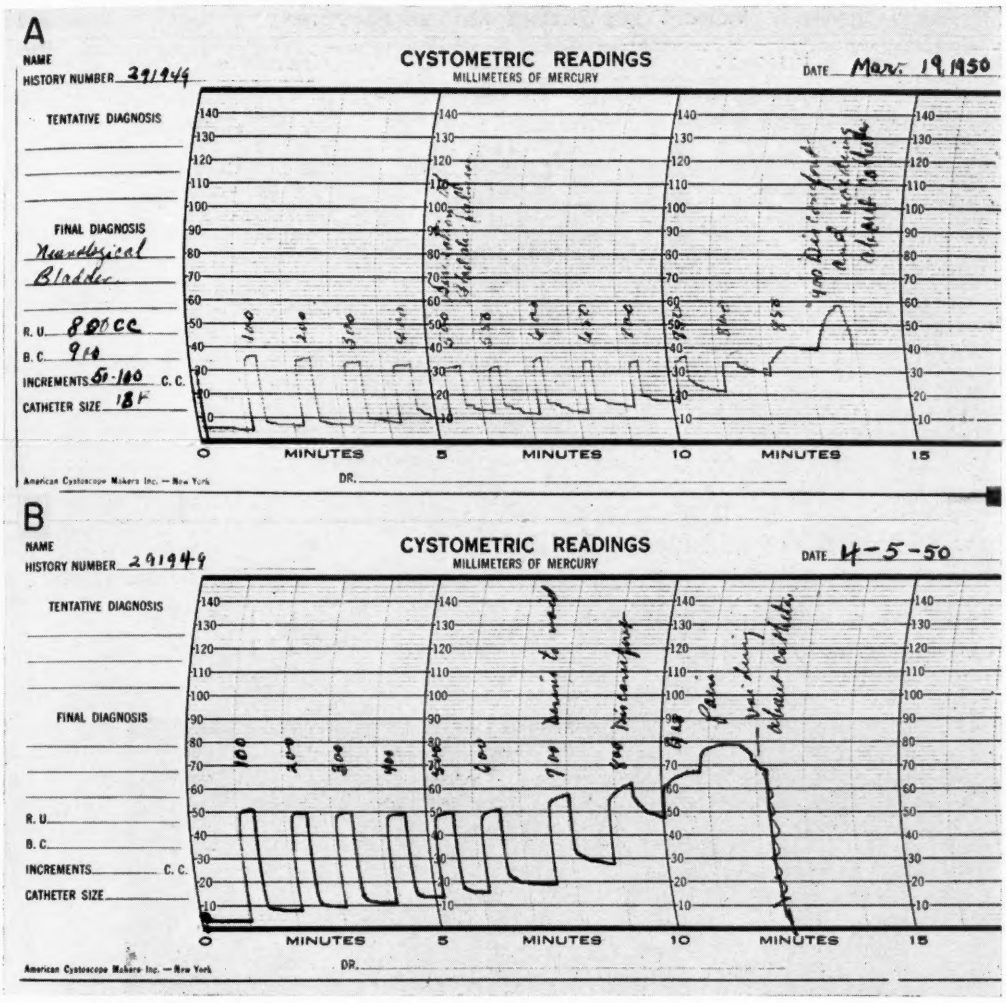

Fig. 6.—Cystometrograms *A*, and *B*, done after an interval of 3 weeks, showing recovery of function of a hypotonic bladder.

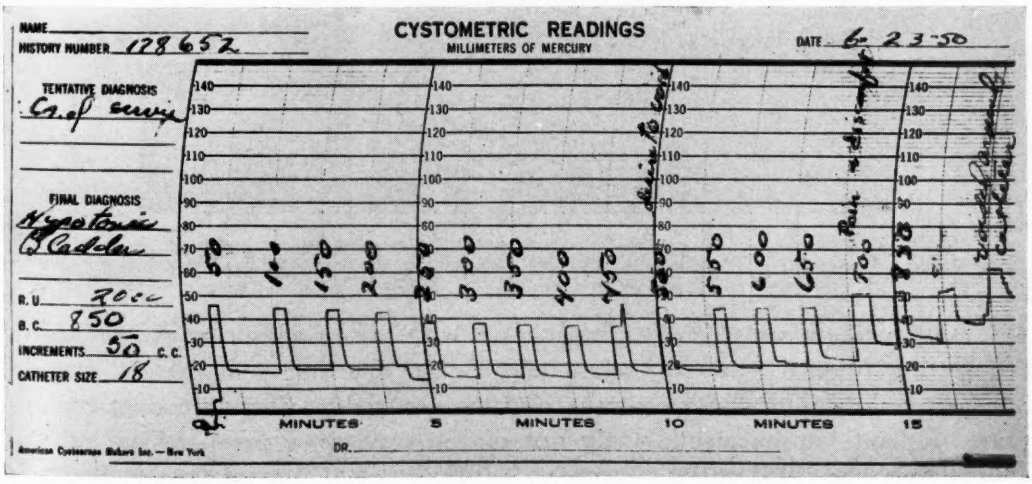

Fig. 7.—Cystometrographic studies done twelve months after operation showing some loss of sensation and hypotonicity. In spite of these findings, this patient was asymptomatic.

TABLE VII. WITHOUT BLADDER SYMPTOMS

INTERVAL	PATIENTS
3 mo.	1
14-20 mo.	3
20-34 mo.	5
40-60 mo.	6
Total	15

TABLE VIII. LATE BLADDER COMPLICATIONS

	INTERVAL	PATIENTS	X-RAY
Urinary retention	2.5- 8 months	2	0
Bed-wetting	5-48 months	2	1
Loss of sphincter control and bed-wetting	15-36 months	4	1
Loss of sensation and incontinence	6-48 months	4	3
Residual urine	24 months	1	0
Total		13	5

bladder and has shown no recovery after four years. Cystograms (Fig. 8) show this contracted and distorted bladder. This patient received preoperative x-ray therapy and this may well be a factor in her extensive pelvic fibrosis. The other patient recovered function after five months and is symptom free two years after operation.

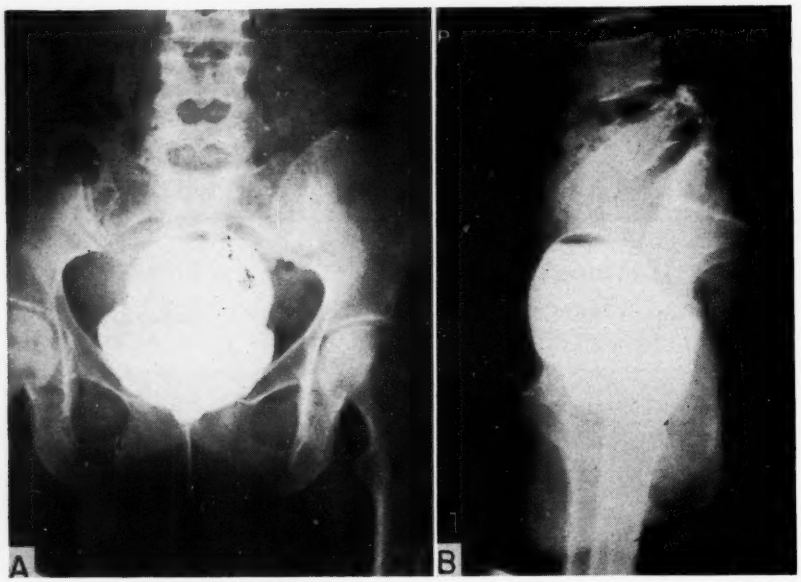

Fig. 8.—Cystograms of a contracted, distorted bladder with pseudodiverticula and loss of sensation. Capacity of 200 c.c. with no loss of sphincter control but a severe bed-wetting problem.

Four patients are severely incapacitated with loss of sphincter control and bed-wetting to such a severe degree that rubber sheeting is necessary. One has been followed for fifteen months, and the other three for more than three years, without improvement. Only one of the 4 received preoperation x-ray and this may be ruled out as a source of difficulty in the other three patients. Cystometrograms show typical hypotonic bladders, and Fig. 9 was confirmed by

electromyographic studies of the bladder. In two of these patients it was felt that fixation of the base of the bladder in the scar tissue of the short vaginal vault might play some part in the urinary sphincter incontinence. The Ball[9] modification of the Marshall-Marchetti[10] urethrovesical fixation was carried out in these two patients with no appreciable improvement. Preoperative and postoperative cystograms (Fig. 10) show correction of the posterior urethrovesical angle[11] and the urethroscopic examination shows a normally functioning sphincter. This group has the most severe bladder difficulties and from a practical standpoint these patients are as incapacitated as those with vesicovaginal fistulas.

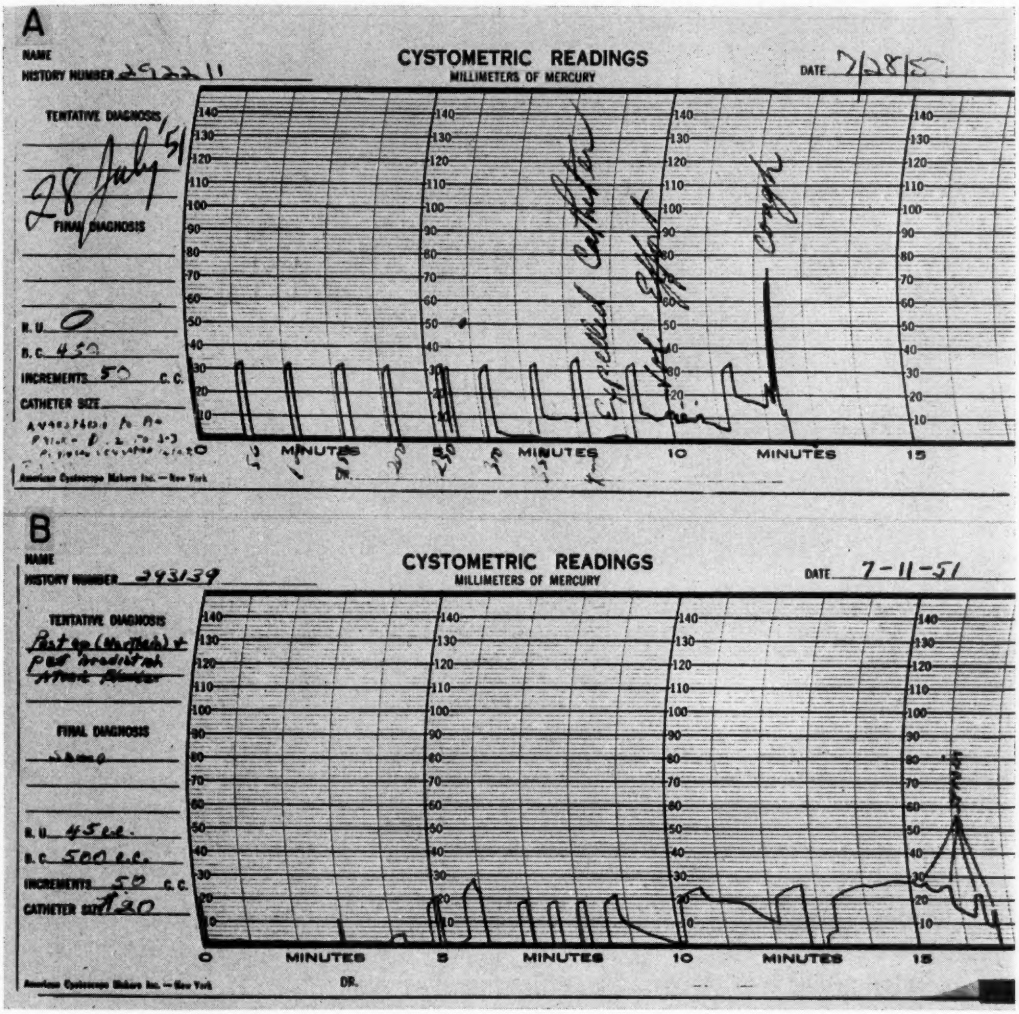

Fig. 9.—Two patients with severe bed-wetting, and sphincter incontinence, with typical hypotonic bladders. No recovery of bladder sensation after 3 years and both remain severe problems. *A*, confirmed by electromyogram.

Four of the 13 patients have been followed from six months to four years with loss of bladder sensation and some sphincter incontinence. Cystograms appear normal and cystometrograms show atonic bladders with loss of sensation. Three of these patients received preoperative roentgen therapy. The remaining

patient in this group of 13 patients with bladder symptoms carried a large bladder residual for nine weeks after operation, after which time she recovered function and is asymptomatic two years later.

It appears that failure to recover bladder function after long periods of time represents faulty parasympathetic innervation as a result of the operative procedure, or damaged bladder musculature with failure to respond to parasympathetic stimulation. A combination of these two factors must also be considered as etiological factors in failure to recover bladder function. Abnormal bladder function is seen in both those treated preoperatively with x-ray and those treated only by radical operation.

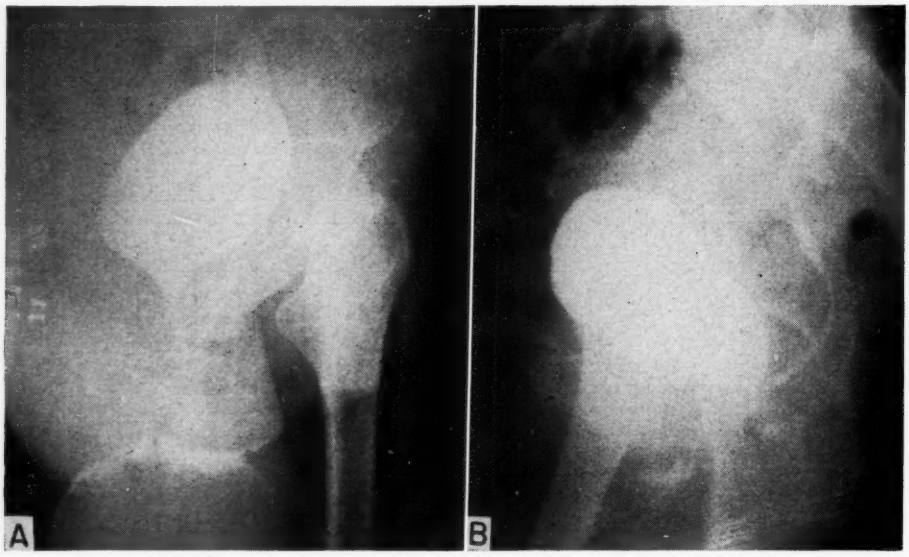

Fig. 10.—*A*, Oblique cystogram prior to combined urethrovesical fixation in an attempt to correct sphincter incontinence and bed-wetting.

B, Postoperative cystogram showing correction of posterior urethrovesical angle without improvement of symptoms.

Comment

It is not with any desire to condemn radical hysterectomy with radical pelvic lymphadenectomy that this small group of patients has been presented. It is my conviction that radical operation has its place in the treatment of carcinoma of the cervix, and with additional experience its proper status will be established.

Urinary tract infections remain a problem in spite of preoperative and immediate postoperative antibacterial agents. Neurological complications of the bladder are one of the most troublesome developments, and in some patients the damage appears to be permanent. Similar bladder changes are seen in patients treated by combined irradiation and operative therapy as well as those treated by operation alone. We have found no satisfactory treatment for a persistent hypotonic bladder.

The upper urinary system complications may be encountered many months after operation, and in most patients they have been silent developments. When

seen in the absence of irradiation therapy, they seem to be secondary to ureteral stricture of intrinsic origin or from fibrosis of the retroperitoneal tissues involving the ureter.

Urological studies are necessary in the follow-up of these patients to detect these complications and to institute treatment prior to the development of renal insufficiency.

I would like to express my appreciation to the members of the Departments of Urology and Roentgenology whose cooperation made these studies possible.

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Discussion

DR. A. W. DIDDLE, Knoxville, Tenn.—Dr. Thornton has given us a thorough, unbiased report. For purposes of comparison with his results, urological complications are reviewed as seen in 23 private patients treated with radical surgery for eradication of cervical cancer between April, 1949, and May, 1953. Nearly three-fourths of these women received irradiation preoperatively and over one-fourth were given no irradiation. The lesion was clinically confined to the cervix (International I) in all but 4 women. Three of these 4 had some extension to the parametria (International II), and the fourth to the floor of the bladder with a vesicovaginal fistula (International IV). Ureteral transplantation was not employed except in the instance of the fistula. Nearly one in 4 patients had spread to the regional lymph nodes.

Care of our patients differed from Dr. Thornton's in these respects: a combination of penicillin and dihydrostreptomycin was begun 48 hours before operation and continued until the bladder catheter was removed or usually about a week postoperatively. Indwelling ureteral catheters were not used.

The urologic complications presumably effected by the surgery were divided into three groups: surgical urinary fistulas, total or partial ureteral compression, and persistent poor bladder control. Three of the 23 women sustained urinary surgical fistulas in the bladder during the operation. These defects were repaired at the time and healed satisfactorily. Still another 6 patients acquired total or partial ureteral compression on at least one side. In one instance total compression was due to metastases. In a second case total block was from failure of the ureteral transplant. In the remaining 4, partial block was attributed to scarring, but ureteral damage is not enough to disturb the blood chemistry and the patients are asymptomatic. The incidence of ureteral compression was the same for irradiated and nonirradiated patients. Finally, another 3 women had poor bladder control for an average of six months. Eleven patients so far have neither early nor late known urinary complications.

Little attention was paid to bladder hypotonicity. The essayist's cystometric studies appear to assure us that this is correct treatment.

Justification for surgical treatment in cervical cancer stems from whether or not fewer complications arise or more patients survive than with irradiation alone. So far, published results are so selective that it is impossible to make a convincing comparison. However, there is a group of patients in whom irradiation is not curative. Note, two-thirds of Dr.

Thornton's patients irradiated preoperatively retained residual viable tumor in the cervix or appended tissues. During the time interval April, 1949, to May, 1953, 48 women with operable lesions (International I) were purposely treated only with x-ray and radium in our practice and the East Tennessee Cancer Clinic as opposed to the 23 treated surgically and mentioned previously. At this reporting more than one-fifth of those given only irradiation have already died while all those treated surgically are living. Only one has evidence of recurrence. Incidentally, this woman had two primary cancers, one of the vulva and one of the cervix. Postmortem examination of those given x-ray and radium alone showed, not uncommonly, that the primary tumor was gone. On the other hand, there were regional metastases beginning below the brim of the pelvis within the field of previous irradiation. It is this finding that leads us to continue to use surgery in selected instances.

This final comment is not to detract from the essayist's fine paper. Yet a remark is offered regarding the phrase "radical hysterectomy." It appears desirable either to modify it with the addition of "and pelvic lymphadenopathy" or use another phrase such as "radical pelvic resection" and do away with the word "hysterectomy." There are a number of physicians who ostensibly misinterpret the meaning of "radical hysterectomy" used alone. On the screen is the picture of a specimen recently removed for eradication of a nonirradiated (International III) cervical lesion. The surgeon purposely did the procedure and was of the opinion that he was doing the radical operation. Neither lymph nodes nor parametrial tissues were excised. There is a cut through the capsule of the cervix exposing the entire length of the carcinoma. This sort of past history was found in 3.5 per cent of 234 women with cervical cancer seen personally in the last 4.5 years.

DR. CLAYTON T. BEECHAM, Philadelphia, Pa.—Dr. Thornton has found the paralyzed bladder to be his most common complication. I have been puzzling over this point since reading the paper and wondering if the essayist has come to any conclusions as to why this should be. It seems to me that if enough blood supply is retained so the bladder doesn't slough, there should be enough parasympathetic nerves to allow for normal bladder function. In an attempt to explain what has happened, I should like to ask Dr. Thornton if he thinks he might not have been overzealous in removing perivesical fatty tissue. This could cause considerable muscular as well as nerve damage. In doing these radical procedures, I do not believe that one needs to strip the ureters and bladder of all surrounding tissue but rather to employ meticulous dissection around the ureterovesical junction and the base of the bladder. We have followed this in our cases and those where we have combined the radical hysterectomy with a radical colpectomy for carcinoma of the vagina. Thus far we have not had any cases of bladder paralysis.

In the last 21 cases we have left ureteral catheters in place for 2 weeks, along with a Foley catheter. It is my feeling that the ureteral dilatation incident to the indwelling catheters maintains good drainage. An unobstructed and dilated ureter would seem less likely to slough and therefore perhaps to reduce the incidence of ureterovaginal fistula. Our cases thus treated have had no urinary problems over an eighteen-month period.

DR. JOE V. MEIGS, Boston, Mass.—I am delighted with Dr. Thornton's paper which I think demonstrates the findings that are characteristic of surgery for cancer of the cervix. Our great problem is that of the ureter and the bladder. Were it not for such complications there would be no question in my mind but that surgery is the best way to treat it. We have struggled with urinary difficulties for a long period of time, and have tried everything we know to prevent the difficulties. If you will go back and read Wertheim's paper, you will find that he had exactly the same problem then that we have today. Navatil of Graz, Austria, has recently been here, and his discussions were about the ureter, what to do with it, and the bladder, and what to do about it. I have on my desk at home an article written by Paul Werner of Vienna, and he has the same difficulty and the same problem. What do we do with the ureter, and how can we prevent difficulty with the bladder? Both these men have suggested using free omental grafts around the ureter.

I have the same difficulty today that I had when I first started in 1939 to do these surgical procedures. Dr. Ulfelder and Dr. Ingersoll, who are my associates, very rarely

have ureteral fistulas, but I do. I don't know whether they are better than I am or whether they don't do it as well as I do. I am sure that the fewer times we traumatize the ureter, the greater care we take of it; the less frequently we put a tape around it or catheters in it, the better. I am sure also that after we learn how to do the surgery we become more and more radical, and I believe that is my difficulty. The dissection along the rectum and deep along the vagina, coming up to the bladder, and the tissue around the entrance of the ureter into the bladder are vulnerable parts for the surgeon. In the deep resection I am sure we injure the nerve supply of the bladder, probably permanently. We have tried draining the pelvis with a Miller wick to no avail. We still use one.

As a result of the cystometrogram studies of Dr. Martin Bellinger at the Pondville Hospital, the Massachusetts State Cancer Hospital, and of Dr. Peter Vandervelde from Belgium, who studied with us in the Vincent Memorial Hospital Laboratory, we think that what happens following the surgery is that at first there is a hypertonic bladder—not hypotonic but hypertonic. At the end of six, seven, eight, or nine days the catheter is removed. Then the patient, having no sensation—and most patients have no bladder sensation following the radical operation—can't tell when her bladder is full; the nurse can't tell when to catheterize; the house officer can't, you can't, and your assistant can't. The patient gets a full bladder. Once the bladder is full, it become hypotonic, and is just like a wet rag. Such a bladder is a long time coming back, if it ever returns to normal. We have patients who have to stand up or squat to urinate four to seven years after the surgery.

On the recommendation of Dr. Bellinger and Dr. Vandervelde we have decided to put a Foley catheter in the bladder and leave it there. Since September, 1952, we have left a Foley catheter in the bladder of every patient for two months after operation. The patient is told not to shut off the catheter for more than one hour at a time. These patients are brought back into the hospital after two months, their catheters are removed, they are catheterized after the first voiding and again the next morning. These patients have bladder tone and can void, but they have no sensation. Since September, 1952, I have had but one fistula, and that was in a patient with extensive disease near and about the ureter, necessitating tying off the internal iliac artery and external iliac vein.

I think that Dr. Thornton's paper has been excellent. He has demonstrated to us the difficulties that we know about. His findings will be typical of practically every one of us who attempts to do this radical type of surgery.

DR. HOUSTON S. EVERETT, Baltimore, Md.—I think Dr. Thornton is to be congratulated for bringing this subject to our attention, because it is a subject that needs to be kept before us as gynecologists. The reason for that is that most of us gynecologists are not urologists, and most urologists are not particularly interested in this subject. Dr. Thornton was fortunate in that one of the urologists at the University of Virginia was a resident gynecologist before he fell from grace. Dr. Meigs has a group in Boston who are interested in the subject and Dr. Archie Deane at the Memorial Hospital has been interested; and so far as I know that just about includes all of the urologists who are really interested in this subject. Hence we have to take the responsibility, and if we don't do our own urology, we have to try to interest our urological associates in the subject.

I began to study, write, and talk about the urological complications following irradiation therapy of carcinoma of the cervix in 1929, and at first I was very much criticized by the radiologists. They felt that I was condemning it as a method of treatment. I never had any such idea, and I don't want to enter into an argument about which is better—radical surgery or radiology. The point is that these urological complications do follow both methods of treatment. I have not experienced as high an incidence of bladder complications as Dr. Thornton reported; but the slowly progressive hydronephrosis can be completely asymptomatic, and the patient can get into the stage of uremia before it is realized what is going on. A patient who has been treated for carcinoma of the cervix by either method should be followed carefully from a urological standpoint as long as she is kept under observation, which should be the rest of her life.

DR. RALPH CAMPBELL, Madison, Wis.—I want to emphasize that in our radical cases—and I assure you that we have done very few—we always put ureteral catheters in; and for Dr. Diddle's consumption, we respect the ureter whether the catheter is in or not. I wish to emphasize further that we leave the ureteral catheters in for several days, as pointed out by Dr. Beecham, and we also leave the retention catheter in the bladder for several days, as pointed out by Dr. Meigs.

DR. THORNTON (Closing).—I want to thank Dr. Diddle for his discussion, and I can appreciate his sentiments in regard to the terminology.

Dr. Beecham, I think we have been a little vigorous in our dissection around the base of the bladder and the vesicoureteral areas, and I feel, as Dr. Meigs expressed it, that as the years go on, it seems that you become a little more radical in your approach to the problem. I believe this may explain some of the bladder difficulties encountered and our high incidence of this difficulty.

SQUAMOUS PAPILLOMAS OF THE CERVIX*†

R. R. GREENE, M.D., AND BEN M. PECKHAM, M.D., CHICAGO, ILL.

(From the Department of Obstetrics and Gynecology, Northwestern University Medical School and of Wesley Memorial Hospital and from the Chicago Maternity Center)

ABOUT two years ago, biopsies were made from the cervix of a patient who clinically seemed to have an invasive carcinoma. Histologically, the tissues appeared to be those of benign papillomas. As will be detailed later, this patient ultimately died from this histologically apparently benign, but clinically invasive carcinoma of the cervix. One year later, we had an opportunity to interpret a biopsy specimen from another patient, which histologically appeared quite similar to the first. Repeat biopsies were requested twice (four-quadrant biopsies each time). Influenced by the findings in the first patient, a hysterectomy was recommended. When the removed uterus was examined a diffuse papillomatosis was found covering the ectocervix, endocervix, and the whole endometrial cavity. The confused findings in these two patients made it evident that we knew little concerning papillomas of the cervix. The present study was therefore undertaken.

Papillomas are defined as neoplastic growths of surface epithelium supported on cores or papillae of vascularized connective tissue. More specifically, in this presentation, we will be limited to those in which the surface epithelium is of the stratified squamous variety. This in itself helps to differentiate such lesions from the usual endocervical polyps of the cervix. In addition, the connective tissue core of papillae is very different from the stroma found in endocervical polyps; even though the latter may be partially or even completely covered with stratified squamous epithelium which has arisen by metaplasia.

Judging from the literature, papillomas of the cervix are relatively rare lesions. In August, 1952, Memoir R. Marsh[4] reviewed the literature on this subject. He found that such lesions had been reported in only 23 patients. He added eight more, making a total of 31. Tissues from 26 patients with such lesions have been prepared in the laboratory of the Department of Obstetrics and Gynecology at Northwestern University. All of these lesions have been discovered since 1946. Ten of them were from private patients and the remainder from the dispensaries of Northwestern University Medical School, the Chicago Maternity Center and Wesley Memorial Hospital.

Marsh's review of the literature was complete. It will not be repeated here. Those interested in a complete bibliography on this subject should con-

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sult his article. Incidentally he could not distinguish microscopically between a condyloma acuminatum and a papilloma of the cervix. In common with most authors, he considered the lesion to be a condyloma if it was associated with other vulvar and/or vaginal papillomas. In his total series of 31 patients, 10 were considered to have condylomas, 18 papillomas, and 3 malignant papillomas.

We, too, are unable to distinguish between a condyloma acuminatum limited to the cervix and a so-called true papilloma. The series to be presented, however, to our knowledge, includes only one patient who also had condylomatous lesions of the vaginal vault, and none with similar lesions of the vulva.

Findings

Because of the large number of lesions to be presented, the use of the case history method would be too lengthy; the findings will, therefore, be presented in tabular form. The various papillomas fell naturally into three different groups: (1) those that were *typical* in all respects; (2) those that were typical but were *associated with other abnormalities of the cervical epithelium;* and, finally, (3) *atypical papillomatous lesions.*

Gross descriptions were available for the majority of the lesions, and most were described as discrete, elevated wartlike areas. However, a few were considered, grossly, to be carcinoma of the cervix. Two were described as discrete white areas with an irregular surface. Microscopically, the latter two lesions were sessile as one would expect.

Certain histologic generalizations are possible, despite the confusing exceptions which will be discussed in some detail later. Microscopic diagnosis is usually simple, since the lesions are branching papillary structures with relatively fine cores, or papillae, containing good-sized blood vessels, and are covered by thick stratified squamous epithelium. Due allowance must be made, however, for tangential and right-angle planes of section in interpreting this papillary appearance. In addition, irregular planes of sections may sometimes give a "tissue invasion" appearance. In most instances, there is moderate infiltration of the cores by chronic inflammatory cells. In many, there were, in addition, acute inflammatory cells. When such cells were present, they frequently also infiltrated the surface epithelium itself. In general, the nuclei were normal except that binucleate cells could be found in almost every lesion. The basal-cell layer is sometimes increased in thickness to two or three layers of cells. This was frequently the case during pregnancy, and we believe signifies rapid growth of the lesion. Mitotic figures were rare and were confined to the basal-cell layer or were immediately above it. In others, where the basal-cell layer was thickened, they could be found in the second or third layers of cells. Mitotic figures were usually normal in appearance, although minor abnormalities were found even in the most benign-appearing papillomas, after diligent search. The architecture was usually normal. In most of the lesions, surface cornification was present. Frequently, however, during pregnancy, glycogenation had taken place, and the cells up to the surface remained fairly large and round and had small pyknotic nuclei.

Typical Papillomas

There were 13 patients with typical papillomatous lesions of the cervix (Figs. 1 and 2). The lesions varied in size from that seen in Patient No. 1 which covered the whole ectocervix (discovered when the cervix was inspected immediately after delivery) to the minute lesions (Patient No. 14) discovered at the external os in a hysterectomy specimen. All were grossly elevated wart-like lesions, except one in a nonpregnant patient (No. 10), which was a 1 cm. discrete, white, slightly elevated area with an irregular surface. Biopsies made from the margin of that lesion revealed a sessile but otherwise typical papilloma.

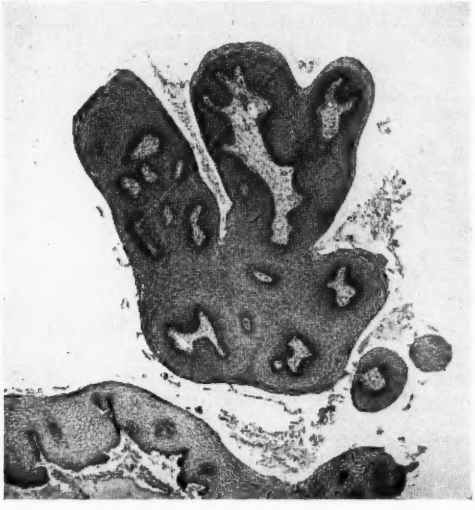

Fig. 1.—N. U. Gyne. 14419. A low power of a typical papilloma from Patient No. 4, showing a moderate degree of surface cornification. (×27; reduced ¼.)

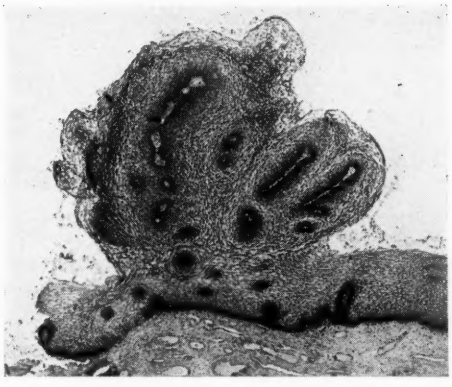

Fig. 2.—N. U. Gyne. 18026. A low power of a typical papilloma from Patient No. 6. The superficial layers of cells are glycogen laden. (×27; reduced ¼.)

Eight of the 13 patients were pregnant and 3 have not yet completed their pregnancies. In one of these, the papilloma disappeared during pregnancy (No. 6); the other 2 will be followed post partum. Four of the 5 lesions followed post partum disappeared (though 2 of these patients were not seen until

over two years later and were then again pregnant). The fifth (No. 5) was minute but still present at eleven weeks post partum but had disappeared at eight months.

TABLE I. TYPICAL PAPILLOMAS

NO. AND NAME	AGE	PREGNANT?	FINDINGS*	REMARKS
1. H. C.	28	Term	(1) Typical papilloma	Cervix grossly normal at 2 months post partum
2. P. R.	26	27 weeks 28 weeks 6 weeks post partum	(1) Typical papilloma (4) Typical papilloma (4) No papilloma	Numerous mitotic figures. At 6 weeks and 6 months post partum, the cervix was grossly normal
3. E. M.	21	26 weeks	(1) Typical papilloma	Patient finally returned, again pregnant, 2½ years later. Cervix grossly normal
4. V. G.	21	16 weeks	(1) Typical papilloma	Did not return for postpartum check. Pregnant again and cervix grossly normal, 2 years later
5. D. J.	35	27 weeks 11 weeks post partum 8 months post partum	(4) Typical papilloma (4) Small but still present (4) No papilloma	Cervix grossly normal at 11 weeks and 8 months post partum
6. J. A.	18	16 weeks 24 weeks	(1) Typical papilloma (4) Papilloma gone	Still pregnant
7. D. O.	21	21 weeks 25 weeks	(1) Typical papilloma (3) Normal epithelium	Second biopsies of other 3 quadrants. Cervix appeared normal. Patient is still pregnant
8. R.	26	16 weeks	(2) Typical papilloma	Still pregnant
9. H. S.	27	No	(1) Typical papilloma	Dilatation and curettage for functional bleeding 5 months later. Cervix grossly normal
10. N. S.	25	No	(2) Sessile papilloma	Biopsies at edge of lesion only. Two weeks later no abnormalities nor at 6 months and 18 months
11. D. L. M.	27	No	(1) Typical papilloma	Cervix cauterized after biopsy, negative appearance 2 and 3 months later
12. M. P.	43	No	(4) Tiny but typical papilloma	Patient was 7 years post-menopausal
13. V. E.	34	No	Typical papilloma	Accidental discovery in operative specimens

*Number in parentheses refers to number of quadrants biopsied.

Of the 5 nonpregnant patients, one papilloma was discovered in a hysterectomy specimen (No. 13); another was cauterized after biopsy (No. 11); and a third patient was subsequently lost. In the remaining 2 (Nos. 9 and 10), the lesions apparently disappeared spontaneously. No. 9 was curetted for dysfunctional bleeding five months after biopsy. The cervix grossly was devoid of papillomas. The lesion, in No. 10 (mentioned above), had completely disappeared two weeks after a biopsy which included only the edge of the lesion. The cervix appeared normal at inspection six and eighteen months later.

Typical Papillomas Associated With Abnormal Cervical Epithelium

Six of the lesions were associated with abnormal cervical epithelium; and of these, 4 were in pregnant patients. The details are given in Table II. Two of these cases (Nos. 14 and 15) have been reported in a previous publication.[2]

TABLE II. TYPICAL PAPILLOMA ASSOCIATED WITH ABNORMAL CERVICAL EPITHELIUM

NO. AND NAME	AGE	PREGNANT?	FINDINGS	REMARKS
14. D. W.	23	16-18 weeks	(1) Typical papilloma with preinvasive carcinoma at its base	This is Patient No. 14 of a previous report.[2] Continuity but no transition between papillomatous and carcinomatous epithelium
		22-24 weeks	(4) Same finding	
		9 weeks post partum	(4) No papilloma but carcinoma same	
		21 weeks post partum	(Hyst.) No papilloma but carcinoma same	
15. M. R.	22	27 weeks	(2) Preinvasive carcinoma	Papilloma appeared between twenty-seventh and forty-ninth weeks. Noted at delivery and removed by wedge excision. This is Patient No. 7 of a previous report[2]
		Delivery	(1) Large papilloma only	
		9 weeks post partum	(4) Equivocal lesion and no papilloma	
		11 weeks post partum	(Hyst.) Preinvasive carcinoma	
16. M. O.	20	27 weeks	(1) Typical papilloma	Papanicolaou smears suspicious. Repeat biopsy requested
		29 weeks	(4) Typical papilloma with adjacent equivocal lesion	
		16 weeks post partum	(2) No papilloma but with adjacent equivocal lesion	
		12 weeks	(Hyst.) Preinvasive carcinoma	Hysterectomy during second observed pregnancy
17. L. A.	18	29-31 weeks	(2) Papilloma with adjacent BCH*	Fourth biopsy done approximately 1 year after third biopsy. Patient being followed
		6 weeks post partum	(1) BCH only	
		12 weeks post partum	(4) BCH only	
		20 weeks pregnant	(4) Normal epithelium only	
18. B. H.	22	No	(4) Papilloma at 3 o'clock, equivocal lesion at 12 and 9	First biopsy on 4-2-52. Repeated 6-4-52, 10-8-52, and 11-1-52. Cone amputation done 11-28-52
			(4) Same findings	
			(4) Preinvasive carcinoma only (minute)	
			(1) Negative	
			(Cone) BCH marked	
19. L. W.	30	No	(4) Typical papilloma and equivocal lesion	No continuity between epithelium of papilloma and equivocal epithelium. Hysterectomy done, 2 weeks after biopsy
			(Hyst.) BCH only	

*BCH = Basal-cell hyperplasia.

Patient No. 14 (also No. 14 in our previous report) had a biopsy during pregnancy because a gross papillomatous lesion was present. A Papanicolaou smear was done at the same time and was reported positive. Six weeks later, four-quadrant biopsies were taken. In both the first and second biopsies, a papilloma was present; and at its base, there was a definite bizarre preinvasive squamous-cell carcinoma of the cervix (Figs. 3 and 4). There was contiguity

but abrupt transition between the malignant epithelium and the benign epithelium of the papilloma. The patient had another biopsy nine weeks post partum. The papilloma had disappeared, but the preinvasive carcinoma was still present. The same preinvasive lesion was found in the serial blocks from the hysterectomy specimen at twenty-one weeks post partum; in one block, minimal invasion was believed to be present.

Patient No. 15 (No. 7 of our previous report) had a biopsy during the twenty-seventh week of pregnancy, because of two previous atypical Papanicolaou smears. Preinvasive carcinoma was discovered in the biopsy. Immediately after delivery, the cervix was inspected and a large papillomatous lesion was noted. This was removed by wedge excision. Only papillomatous tissue was present in this biopsy. Apparently, the papilloma developed between the twenty-seventh and the fortieth week (at which time she delivered). At nine weeks post partum, no papilloma was present grossly and there was no evidence of papilloma in the four-quadrant biopsies either; however, an equivocal lesion was present. At eleven weeks post partum, a hysterectomy was done, and preinvasive carcinoma was present in the hysterectomy blocks.

Fig. 3.

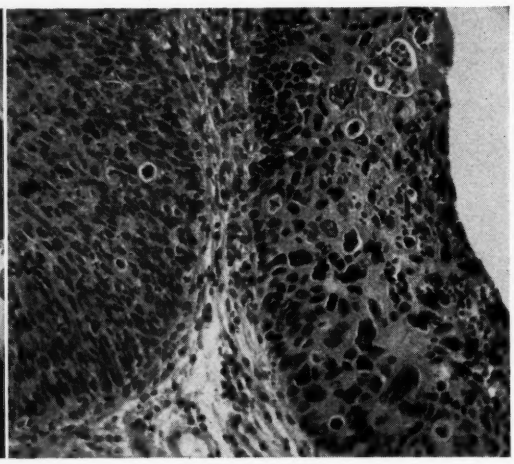

Fig. 4.

Fig. 3.—N. U. Gyne. 14836. A low power of a typical papilloma in Patient No. 14. The arrow points to adjacent bizarre preinvasive carcinoma. (×10; reduced ¼.)

Fig. 4.—N. U. Gyne. 14836. A high power of the carcinomatous area from Fig. 3. (×220; reduced ¼.)

Two other patients had papillomas and abnormal cervical epithelium during pregnancy. The first, No. 16, had a biopsy taken at the twenty-seventh week of pregnancy, because of a gross papilloma. At the same time, a Papanicolaou smear was made and reported as suspicious for malignant cells. Two weeks later, four-quadrant biopsies were made and adjacent to the papillomatous tissue there was an equivocal lesion. The findings were distinctly abnormal, but were considered inadequate to justify the diagnosis of carcinoma. At sixteen weeks post partum the biopsies were repeated; no papilloma was present in the biopsies and none was described in the gross findings. The equivocal lesion, however, was still present. During the twelfth week of the next pregnancy, a hysterectomy was done and a preinvasive carcinoma was found in the serial blocks of the cervix.

The next patient (No. 17) had a biopsy because of a gross papillomatous lesion during the twenty-ninth week of pregnancy. In the immediately ad-

jacent cervical epithelium, a basal-cell hyperplasia with nuclear atypia was present. Six weeks post partum there was no gross lesion, but biopsy showed similar basal-cell hyperplasia. At twelve weeks post partum, four-quadrant biopsies were made and, again, basal-cell hyperplasia was present. This patient is now pregnant again and at the twentieth week no gross papillomas are recognized on the cervix; furthermore, in the four-quadrant biopsies neither the papilloma nor basal-cell hyperplasia were found.

The remaining 2 patients in this group were not pregnant. The first (No. 18) had a biopsy because of a gross papillomatous lesion and a positive smear. Four-quadrant biopsies were taken. A papilloma was present at 3 o'clock, and an equivocal lesion was present at 12 and 9 o'clock. Two months later the four-quadrant biopsies were repeated and there were similar findings. Four months later, the biopsies were repeated; the papillomatous lesion was no longer present but a minute area of preinvasive carcinoma was found in one of the four quadrants. Three weeks later a single biopsy was made, and the findings were negative. A cone amputation of the cervix was performed three weeks after the last biopsy. No papilloma was present, but a marked basal-cell hyperplasia with nuclear atypia was found; however, the findings were insufficient to justify a diagnosis of carcinoma.

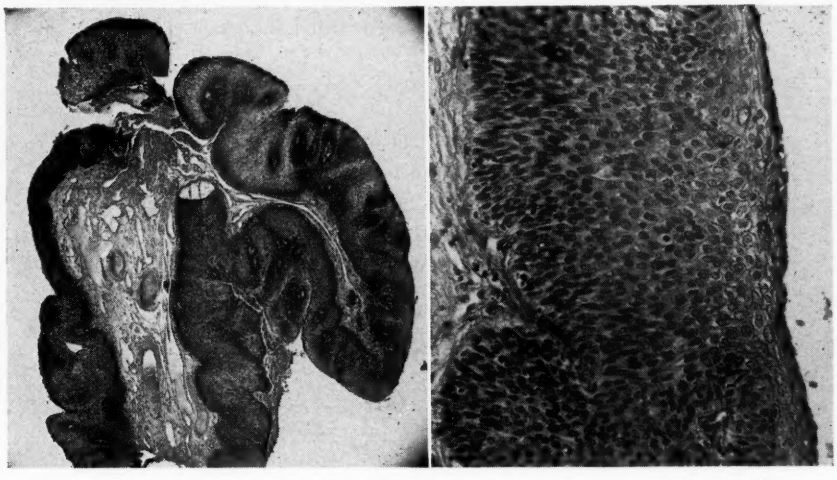

Fig. 5. Fig. 6.

Fig. 5.—N. U. Gyne. 17422. A low power of the lesion from Patient No. 22. Marked atypical basal-cell hyperplasia, or possibly an equivocal lesion, is present both in the epithelium of the papilloma and in the adjacent cervical epithelium. (×16; reduced ¼.)

Fig. 6.—N. U. Gyne. 17422. A high power of the adjacent epithelium in Fig. 5. Seven months later the papilloma had disappeared and the cervical epithelium was normal. (×200; reduced ¼.)

The last patient (No. 19) had a typical papilloma and also an equivocal lesion in the cervical epithelium. There was a strip of normal epithelium between the equivocal area and the papillomatous area. A hysterectomy was done two weeks after the biopsies. The hysterectomy specimen contained only a basal-cell hyperplasia with nuclear atypia.

Thus, in the pregnant patients the papillomas disappeared post partum but the associated more clinically significant lesion did not (the basal-cell hyperplasia was found post partum in Patient No. 17 but could not be found during the next pregnancy). In the first of the nonpregnant patients (No.

18) it seems probable that no papilloma could have survived the numerous biopsies. In the other nonpregnant patient (No. 19) the original biopsy was taken in the operating room and the lesion was probably completely excised.

Atypical Papillomatous Lesions

There were 7 patients in this group (Table III). In 5 (3 of whom were pregnant), the papillomatous epithelium showed basal-cell hyperplasia or equivocal changes insufficient for the diagnosis of carcinoma (Figs. 5 and 6).

TABLE III

NO. AND NAME	AGE	PREGNANT?	FINDINGS	REMARKS
Abnormal Epithelium in Papilloma.—				
20. E. G.	32	No	(2) Marked BCH* in epithelium of papilloma, slight BCH in adjacent epithelium	Cervix cauterized after biopsy
			(1) Slight BCH, no papilloma	4½ months after 1st biopsy
			(2) Slight BCH, no papilloma	3 years after 1st biopsy
21. E. T.	23	No	(2) Sessile papilloma with BCH and marked surface keratinization adjacent epithelium normal	No follow-up available
22. K. Y.	19	20 weeks	(1) Marked BCH or equivocal lesion (?) in papilloma and continues into adjacent nonpapillomatous epithelium	
		23 weeks	(1) Same findings	
		8 weeks post partum	(4) No papilloma. Epithelium normal	Patient being followed
23. E. C.	31	15 weeks	(1) Marked BCH in papilloma. No nonpapillomatous epithelium in biopsy	Being followed. To have biopsy after delivery
24. W. M. B.	22	27 weeks	(1) Moderate BCH in papillomatous epithelium. None in adjacent epithelium	To be followed
		31 weeks	(3) Same findings	
Invasive Papilloma.—				
25. M. P.	45	No	(2) Histologically benign papilloma	Grossly a fungating carcinoma of the cervix
			(2) Benign papilloma with invasion of tissues by cords and masses of fairly normal cells	Patient died. Invasive carcinoma 10 months after appearance of lesion
			(2) Same	
Diffuse Papillomatosis.—				
26. W.	64	No	(1) Papilloma with BCH and hyperkeratinization	No or little underlying stroma in first 2 sets of biopsies
			(3) Same	
			(4) Same plus possible carcinoma (?)	
			(Hyst.) Diffuse papillomatosis of ectocervix, endocervix and endometrium	
			(2) Granulations of vaginal vault	4 months postoperative

*BCH = Basal-cell hyperplasia.

The sixth, though microscopically benign, invaded the tissues and caused the death of the patient. The last, also microscopically benign, covered the ectocervix, endocervix and endometrium but did not invade the tissues.

Of the first 5, two of the pregnant patients (Nos. 23 and 24) are undelivered and are being followed. The third pregnant patient (No. 22) had no papillomas at eight weeks post partum and the cervical epithelium microscopically was normal. Of the nonpregnant patients one (No. 20) had a thorough cauterization of the cervix at biopsy; and though a slight basal-cell hyperplasia persisted, no papillomas were subsequently found at four and one-half months and three years. The other (No. 21) nonpregnant patient is unfortunately not available for follow-up study.

The adjacent nonpapillomatous epithelium in Patient No. 22 was involved in the abnormal (equivocal) epithelial change (Fig. 6). This was true in two consecutive biopsies made in pregnancy, but as stated above no abnormality was found in the postpartum biopsies. In nonpregnant Patient No. 20 there was slight basal-cell hyperplasia in the adjacent epithelium. This abnormality persisted in subsequent biopsies. In the remaining 4, the adjacent epithelium was normal in 2 and not obtained in 2.

Fig. 7.

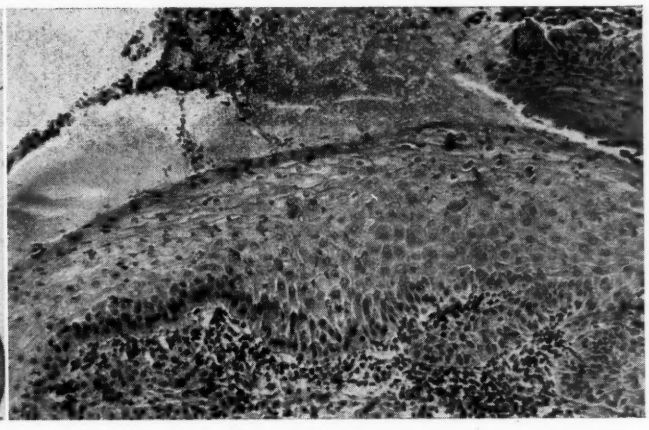

Fig. 8.

Fig. 7.—N. U. Gyne. 15278. From the first biopsy, Patient No. 25. This was interpreted as an "atypical condyloma acuminatum." (×35; reduced ¼.)

Fig. 8.—N. U. Gyne. 15278. A high power from the same field as in Fig. 7. The architecture and nuclei seem normal. The epithelial "penetration" of the stroma was believed to be due to the tangential plane of the section. (×120; reduced ¼.)

The next patient (No. 25) was admitted to the hospital because of an apparent grossly invasive carcinoma of the cervix. The cervix had been inspected three months prior to this admission. At that time, no gross lesion was recognized. Multiple biopsies were made of the lesion and there was much discussion and argument about their interpretation. Both of us were certain that this was a benign papillomatous lesion. A diagnosis was made at that time of an atypical condyloma acuminatum of the cervix (Figs. 7 and 8). An attempt was made to do a hysterectomy. However, there was so much induration in the base of the broad ligaments that only a supracervical hysterectomy and bilateral salpingo-oophorectomy could be done. Following surgery the patient was given various antibiotics and sulfonamides for a

period of two months. During this period, the cervix appeared to be shrinking. No bleeding occurred even on a digital examination until four months later. At this time, the cervix appeared to be smaller, but the fornices of the vagina appeared to be invaded and partially obliterated. She was, accordingly, readmitted to the hospital and cervical biopsies were repeated (Figs. 9 and 10). At this time, the diagnosis was made by us of an invasive well-differentiated squamous-cell carcinoma of the cervix probably arising in a squamous-cell papilloma of the cervix. Others, however, continued to believe

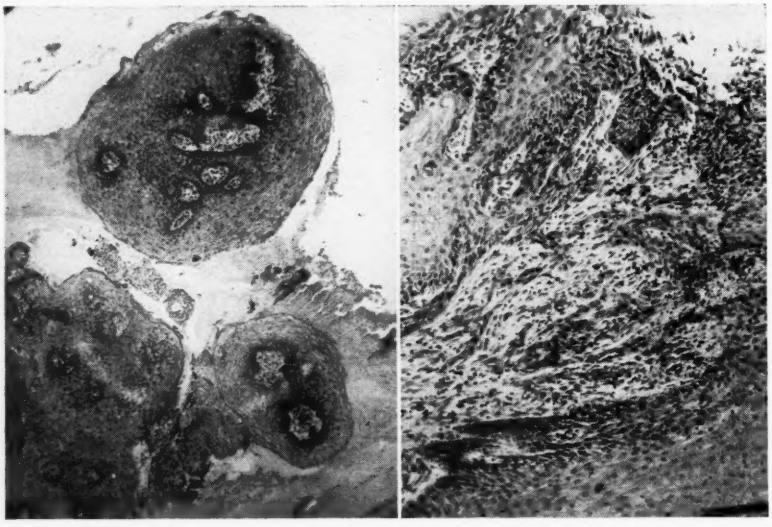

Fig. 9. Fig. 10.

Fig. 9.—N. U. Gyne. 15766. From the second biopsy on Patient No. 25. In this field the tissue resembles a benign papilloma. (×35; reduced ¼.)

Fig. 10.—N. U. Gyne. 15766. Another field from the same patient. There is invasion of the stroma by masses and cords of epithelial cells.

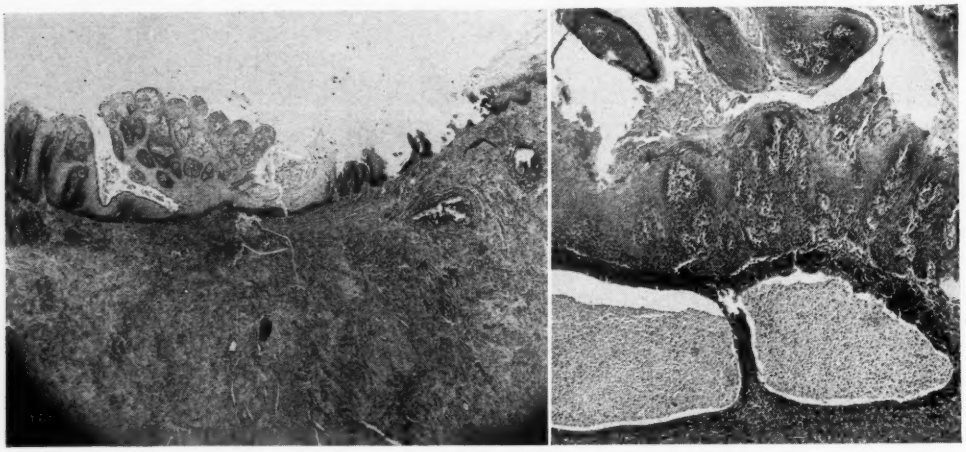

Fig. 11. Fig. 12.

Fig. 11.—N. U. Gyne. 17314. Multiple papillomas covering the endocervix of Patient No. 26. (×21; reduced ¼.)

Fig. 12.—N. U. Gyne. 17314. Papillomas covering the surface of the endometrium in the same patient. Two cystically dilated endometrial glands are included in the field. There is a marked infiltration of the stroma by inflammatory cells. (×49; reduced ¼.)

it to be a "squamous-cell papilloma, the seat of acute and chronic inflammation." The patient was, however, given a course of deep x-ray therapy followed by local radium treatment. Following this, she grew progressively worse, entered the hospital again two and one-half months after completion of radiation treatment, and ten months after the first appearance of the gross lesion. She died one week later. Postmortem was not permitted. In retrospect, it is obvious that an invasive lesion was present in this patient at the time of the first biopsy and that our diagnosis was not only completely erroneous but it unfortunately delayed proper treatment of the patient.

The last case in this series (Patient No. 26) is almost as interesting. The first biopsy submitted to this laboratory contained papillomatous tissue with some basal-cell hyperplasia and hyperkeratinization of the surface but it did not include any of the underlying stroma. Four-quadrant biopsies were requested. In the latter, the findings were confusing and reminiscent of those of the previous patient. Four-quadrant biopsies were, therefore, again requested. The findings were the same with the addition of penetration of the tissues by tongues of epithelium which probably were elongated rete pegs, but which at the time were judged to be possible very early invasion. Because of this and after the patient had an extensive antibiotic treatment for an associated pelvic abscess, a hysterectomy and bilateral salpingo-oophorectomy were performed. A dense-walled sterile tubo-ovarian abscess was found at surgery. In the hysterectomy specimen, there was a diffuse papillomatosis covering the ectocervix, the endocervix (Fig. 11), and the complete endometrial surface (Fig. 12). Four months later, "papillary" structures were noted in the vaginal vault. These proved by biopsy to be merely granulation tissue. The findings in this patient remind one of those reported by Dr. Marsh in his Patient No. 1, except that there was no invasion of underlying myometrium in our patient. To date (one year postoperatively) there is no evidence of recurrence or extension of the lesion.

Comment

As stated in the introduction, this study was stimulated by our lack of knowledge concerning papillomas of the cervix. Unfortunately, we are still ignorant concerning some aspects of this problem. For example, we are not certain that we will be correct in the future in determining whether one of these lesions is necessarily benign or malignant.

Self-Limitation or Spontaneous Regression.—

It seems obvious that most of these lesions are self-limited; that is, if let alone they would probably disappear spontaneously. This certainly seemed to have been true of most of those that were discovered during pregnancy. Some of them, of course, may have been removed completely in the biopsy or destroyed by the inflammatory reaction following the biopsy. It is hard to believe that either of these would be true, however, with the very large lesions, as, for example, in Patient No. 1, in whom the whole ectocervix was covered by multiple confluent cauliflower-like growths. Yet, two months later the lesion had completely disappeared and the cervix seemed grossly normal. Nine patients in this series were pregnant and had adequate follow-up. One of these papillomas disappeared during pregnancy (No. 18); another was probably removed in a wedge excision at term (No. 15); another patient (No. 10) still had a small papilloma at 11 weeks; but at 8 months it had disappeared.

In the remainder, the papillomas had disappeared at the time of postpartum examination. The foregoing applies only to papillomas in pregnant patients in which the epithelium of the papilloma seemed normal (although 3 of them were associated with adjacent abnormalities in the nonpapillomatous cervical epithelium). Another patient (No. 22) had a papilloma during pregnancy in which there were marked abnormalities both in the epithelium of the papilloma and in the adjacent nonpapillomatous epithelium. In spite of these apparent abnormalities, at eight weeks post partum the papilloma as well as the abnormalities in the adjacent epithelium had disappeared. Two other patients with papillomas discovered during pregnancy and with similar abnormalities of the epithelium are being followed at the present time.

The propensity of papillomas to disappear is apparently not limited to pregnant patients. Disappearance of the papilloma in nonpregnant Patients Nos. 9 and 10 has already been cited. In the remaining nonpregnant patients the lesions were destroyed by cautery, or were removed surgically. Patient No. 18 is an exception. Her cervix, however, was subjected to 3 sets of four-quadrant biopsies. The lesion disappeared between the second and third biopsies. It seems likely that the papilloma was removed by these procedures.

On the other hand, not all papillomas disappear or are self-limited. The papillomatous process apparently continued in Patient No. 26, so that eventually, she had a papillomatosis of the ectocervix, endocervix, and endometrium. It is remotely possible that in Patient No. 25 the papillomatous process originally could have been benign, becoming invasive only as it progressed. Of course, this is pure conjecture.

Relation to Other Cervical Abnormalities.—

We suspect that the association between benign papillomas and preinvasive carcinoma, basal-cell hyperplasia, or equivocal lesions, is largely if not completely coincidental. Certainly, this seems true in the Patients Nos. 19, 17, and 15 in whom there was no continuity betweeen the epithelium of the papilloma and the abnormal epithelium. In the remaining 3 patients, there was contiguity between the adjacent lesion and the papilloma but the transition between normal and abnormal epithelium was abrupt. There was no gradation between one and the other.

Relation to Pregnancy.—

Marsh believed that the relationship between papillomas and pregnancy is a very dubious one, since "pregnancy is so frequent and papillomas so rare." In the 31 cases, including his own and those from the literature, 16 of the patients were pregnant. He suggested that this apparently high incidence "may be a reflection of the fact that many women in the childbearing ages rarely are examined vaginally, until amenorrhea compels them to seek additional corroborative evidence of pregnancy from a physician." In our own series of 26 patients, 15 were pregnant and 11 were not. Our data, however, are weighted since much of our material is from the Chicago Maternity Center where the vast majority of patients are pregnant. Eleven of the 26 patients in this series were from the Chicago Maternity Center and all were preg-

nant. Fifteen of the patients were not from the Chicago Maternity Center. Five of them were either from the Northwestern University Medical School Gynecologic or Obstetric Dispensaries or from Wesley Memorial Hospital Maternity Dispensary. One of this group was pregnant. The remaining 10 were private patients of members of the Department of Obstetrics and Gynecology of Northwestern University Medical School. Only 3 of the 10 were pregnant. It therefore seems probable that papillomas of the cervix have no particular predilection for the pregnant individual. Our data are, however, too limited to permit definite conclusions.

It does seem probable, however, that papillomas of the cervix grow larger in the pregnant than in the nonpregnant patient. We have no exact measurements of the gross size of these lesions, but from the descriptions furnished with the biopsies this seems to be true. There is a marked increase in the vascularity of the cervix during pregnancy. It seems logical that the increased blood supply would encourage more rapid growth and lead to increased size. Evidence that papillomas of the cervix grow more rapidly in the pregnant woman has been presented by Edmondson, Levi, Evans, and Horn.[1]

Resemblance to Carcinoma.—

As previously mentioned, a few of these lesions were grossly suspected of being carcinomas. Also as previously stated irregular planes of the section may cause a resemblance to tissue invasion by the epithelial elements. Hill[3] has reported an instance of such a lesion discovered near term in a patient who was subsequently subjected to cesarean section. There was much confusion among pathologists in the interpretation of this lesion, although one of four suggested that it was a papilloma. At 6 weeks post partum it had disappeared. Mershon[5] has reported two instances, one immediately postabortive and the other in pregnancy, in which radium was used. Edmondson, Levi, Evans, and Horn[1] reported 6 cases of papillomas of the cervix. One of these had previously been reported by Mershon, but in another radium was used nine days post partum because there was a lesion grossly thought to be carcinoma. Microscopically, however, it was a typical papilloma. One of us has personal knowledge of another patient who was subjected to cesarean section at term because of a gross lesion believed to be carcinoma of the cervix. Biopsy at that time, however, proved it to be a papilloma. Unfortunately, we do not know the subsequent course in this patient.

Treatment.—

In our experience papillomas of the cervix discovered during pregnancy have been benign and self-limited lesions. This has been true even of one in which there were disturbing changes in the epithelium. We hope it will be true of two more such lesions with abnormal epithelium in patients who are still pregnant at the time this is being written. We have deliberately not recommended treatment of any of the papillomas since we wish to know what would happen to them. Whether they would be responsive to the lytic effects of podophyllin is not known to us.

When these lesions, though of benign appearance themselves, have been associated with abnormalities of the adjacent squamous epithelium (preinvasive carcinoma, equivocal lesions, etc.) these more serious abnormalities have persisted in spite of the disappearance of the papillomas. In such cases obviously the decision as to management must be based on the extent and appearance (microscopically) of the adjacent lesion, not on the benign and probably unrelated papilloma.

The handling of nonpregnant patients with papillomas has largely been beyond our control. At least two of the lesions disappeared spontaneously. Whether others would pursue a similar self-limited course is not known. We do know, however, that the lesions in two other patients did just the opposite. One invaded and killed the patient. Another involved the whole cervix and endometrium.

In the actual handling of any patient with such lesions, biopsies are, of course, necessary. Most patients can be treated conservatively. Certainly, local excision is all that is necessary. However, it seems obvious that the report from the laboratory is *not* the final answer in all instances. The clinical findings, such as extent of the lesion and evidences of gross invasion, are the important factors in determining what should be done. If the lesion is grossly invasive carcinoma it must be treated as such.

Summary and Conclusion

The findings in 26 patients with papillomatous lesions of the cervix have been presented. Usually such lesions are self-limited. The histopathologic diagnosis in most instances is relatively simple. In others, the microscopic findings can be most confusing and may not coincide with the patient's subsequent clinical course.

Addendum.—Due to our carelessness, excellent articles on squamous-cell papillomas of the cervix by J. L. Goforth (South. M. J. **45**: 921, 1952, and Texas J. Med. **49**: 81, 1953) were not cited. Data on 21 such lesions were presented.

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Discussion

DR. ROBERT L. FAULKNER, Cleveland, Ohio.—It is assumed that the authors are writing about squamous-cell papilomas of the cervix. I feel this would be more exact terminology.

The term "papilloma" has become a name applied to a multitude of projecting epithelial lesions in various parts of the body and is used differently by different people. I think this is not a correct practice and believe that this paper adds to and does not detract from this confusion. It is apparent that under this heading the authors include some ordinary papillomas, a few condylomata acuminata, and at least one exophytic squamous-cell car-

cinoma. The authors' insistence that papillomas cannot be distinguished histologically from the soft wart, or condyloma acuminatum, is something which would not appeal to many good skin pathologists who are very insistent that they can make the distinction in the majority of instances. In other words, it does not seem that this term should be used as a waste-basket for any and all projecting squamous-cell lesions of the cervix. Certainly, it is not the name to apply to a lesion which, as in Case 25, killed the patient and was clinically a carcinoma.

Although having been sent sections from and having otherwise seen through the years many projecting squamous-cell lesions of the cervix, I have not had the good fortune to see multiple lesions extending high into the uterus as in Patient No. 26. It is noted that this patient had a severe pelvic infection. Do the authors think the presence of this infection had anything to do with the epithelial changes found?

It is hoped that this publication will not excite undue preoccupation with, and radical treatment for, squamous-cell lesions of the cervix merely because they project. Certainly they and the cervix itself should be biopsied and, if indicated, conization of the endocervix carried out, but it does seem that cytological and histological criteria of the malignant character of any given lesion should be maintained as in the past, and definite treatment carried out as indicated from the findings clinically and histologically and not through fear.

DR. ROBERT A. ROSS, Chapel Hill, N. C.—All recognize the histopathologic studies of the authors as scrupulous critical reporting. This presentation is no exception. They have simplified the present discussion by limiting their studies to "squamous-celled" papilloma of the cervix and report 26 cases. They have divided these patients into 3 groups: 13 typical papillomas, 6 typical papillomas associated with abnormal cervical epithelium, and 7 atypical papillomatous lesions.

Certainly papillomatous lesions as described are frequent within and over the human body. The rather astonishing thing is that they are not more frequently diagnosed on the cervix uteri. Here we have the usual causes for such growths with epithelium of varying cell types, infection, irritation, hormonal influence, and, in pregnancy, hyperemia, laceration, and involution. In pregnancy the cervix should be the ideal site and we believe the authors' figures substantiate this premise.

The pregnant cervix is usually inspected antenatally only once or twice unless the patient has vaginal bleeding. In the nonpregnant patient who has any pelvic symptoms it is inspected more frequently. Tissue is removed for biopsy study much more often in the nonpregnant patient. Cytologic studies, except special studies, are probably more frequently employed in the nonpregnant woman. Unfortunately we have not had the time, since hearing of the authors' findings, to review our own series or the series at Duke, but in these two institutions where pregnant and nonpregnant women are examined by the same doctors, it is the consensus that papillomatous or papilloma-like lesions occur much more frequently in the pregnant patients. In cytologic studies the bizarre is certainly more common in the pregnant woman.

It is difficult to dissociate intraepithelial carcinoma from this discussion. In spite of their positive statement the authors in their "abnormal cervical epithelium" and "abnormal papilloma" groups are concerned with intraepithelial carcinoma. In routine cytologic study of vaginal smears in over 5,000 patients we found, and verified by tissue examinations, only 50 intraepithelial carcinomas. In the authors' series of 26 patients this lesion and questionable pathological findings were relatively much more frequent. At this stage of our knowledge of this particular lesion we should not be categoric.

We should like to ask the authors if they have reviewed virus studies in the development of papilloma. Beard, at Duke, in his broad experimentation with viruses has been able to produce papillomas in his animals. Most of the lesions are in the breast. The histology is quite interesting; some have been typical of malignancy.

DR. LOUIS M. HELLMAN, Brooklyn, N. Y.—I would like to add one word to say that the patient referred to by Dr. Greene as Dr. Marsh's patient died approximately eighteen

months after the lesion was first found. This lesion was originally diagnosed as benign, but, as he said, it grew through the wall of the uterus. Her death apparently was due to extension of this tumor into the abdominal cavity without any remote metastases.

DR. GREENE (Closing).—I thank the discussants for their kindness. First, I shall in the future say "squamous-cell papillomas," not "squamous papillomas." In reply to Dr. Faulkner's question as to whether any of these lesions were just the ordinary multiple condylomas coincidentally on the cervix, the answer is no. One of these patients had adjacent lesions on the vaginal epithelium. To the best of our knowledge none had multiple condylomatous or papillomatous lesions of the vulva. I personally am unable, however, to distinguish under the microscope a condylomatous lesion from the ordinary typical single papilloma of the cervix, and that apparently has been a difficulty reported by almost everybody in the literature.

Whether the infection in the uterus of Patient 26 caused the squamous-cell papillomatosis of the endometrium, I do not know, but I doubt it. This patient also had a diffuse papillomatosis of the endocervix and ectocervix.

Dr. Ross believes that papillomas of the cervix have a predilection for the pregnant patient. Almost everybody in the literature agrees with him except Dr. Marsh. Our figures do not support this belief. Eleven of our patients were from the Chicago Maternity Center. They were all pregnant. Fifteen of the patients were not from the Chicago Maternity Center. Only 4 of these 15 were pregnant. One would expect those from the Maternity Center to be pregnant, but, if we drop those, we have only 4 out of 15 who are pregnant. I still think that the apparently higher incidence during pregnancy is due to the fact that more pregnant patients are being carefully examined.

I am only moderately familiar with the virus studies mentioned by Dr. Ross. There is one recent study in which they were able to find inclusion bodies in the nuclei of a certain percentage of papillomas of the surface skin. I tried to do that with ours, but my findings were too uncertain and varied too much from day to day to be included in this presentation.

SOME FACTORS INFLUENCING THE PROLIFERATION OF THE RESERVE CELLS IN THE HUMAN CERVIX*†

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PRECEDING studies by this group of investigators and others concerning the human cervix during periods of endocrine stress, now extending back over several years, have pointed out a number of interesting but unrelated facts and a few inconsistencies in our knowledge of this organ particularly as related to the morphology of the endocervical canal.[1, 2, 3]

First, it appeared that there were pathological changes in the cells of the endocervix during pregnancy which were indistinguishable from carcinoma in situ and yet which were reversible.[1, 2] This concept engendered some controversy which in essence concerned itself largely with semantics, namely, whether any lesion correctly labeled carcinoma could ever be reversible.[4-8] It was, however, generally affirmed that certain atypical changes occurred in the cells of the endocervical canal during pregnancy which frequently disappeared during the puerperium. This fact was well substantiated in three cases recently exhibited by Greene[9] at the meeting of the American Medical Association in New York. One particular point seems to have received less attention than it deserves, namely, that while the majority of the atypical changes in pregnancy occur within the canal, those described as carcinoma in situ in nonpregnant individuals are stated to occur more frequently on the ectocervical side of the squamocolumnar junction.

Second, rather marked proliferation occurred not only in the glands but actually in the mucus-secreting cells themselves. Studies of the fetal cervix demonstrated a striking similarity between changes which occur in the cervix of the pregnant adult and those in the newborn infant. These changes also were thought, to a certain extent, to be reversible and were, at least on circumstantial evidence, deemed to be related to high estrogen levels present at this period. Such morphological alterations fell under the general heading of epidermization and/or metaplasia. The old controversy as to the origin of these phenomena, whether from ingrowth of the ectocervix[10] or from metaplasia of the mucus-secreting cells, or from groups of endocervical basal cells, failed to clarify their etiology. Furthermore, separate and different entities such as proliferation of reserve cells, hyperplasia of reserve cells, adenomatous hyperplasia, and hyper-

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Fig. 1.—Cervix of newborn.
A, Reserve-cell proliferation.
B, Reserve-cell hyperplasia.
C, Adenomatous hyperplasia of reserve cells.
D, Atypical hyperplasia of reserve cells.

plasia with atypical changes were all lumped together under one heading or another without any clear understanding as to their true nature. At least one fact appeared certain, however, namely, that those changes occurring under the general heading of epidermization were in no way related to malignancy.[11, 12] A better understanding of the process was derived from the description of the frequency of occurrence and the multipotential quality of the endocervical basal cells by Carmichael and Jeaffreson.[13, 14] There was some difference of opinion as to whether these cells were true primitive cells or merely modified stromal cells.[15] The former concept is more likely to be correct, for when there is no active proliferation of the basal cells they are always found above the basement membrane, if present (Figs. 1 and 2, *A*). The group of investigators associated with Dr. Pund in Augusta, Ga., have been studying these cells for a number of years, not only as they occur in the cervix, but also in other structures such as the lung, esophagus, hymen, and so forth.[16, 17] They not only are impressed with the multipotential quality of these cells but have demonstrated quite convincingly that they can become malignant in all structures where they occur.[18] Lee Howard and co-workers[19] first assigned the term "reserve cell" to them as they occur in the cervix. We[3] have adopted this term believing it best expresses the multipotentialities exhibited by these cells.

The rather extensive experimental work on animals is of interest in light of the findings reported in this essay. Overholser and Allen[20] injected six ovariectomized monkeys with 50 to 100 rat units of estrin for 60 to 90 days. The cervices of these animals were also traumatized once a week. One additional animal received the hormone but no trauma and served as a control. So marked were the metaplasia and stromal invasion that such an authority as Ewing thought the changes were "early but definitely established carcinoma." It is interesting to note that trauma probably played little role as the control animal showed more marked abnormalities than did the others. This work was repeated by other investigators with the same results.[21, 22, 23]

It is now generally agreed that the estrogen-induced changes in the monkey are neither cancer nor its precursor. In reviewing some of this material it is apparent to us that the response is one of marked proliferation of reserve cells with squamous metaplasia. The tendency of these cells to undergo squamous metaplasia in the monkey is extraordinary. Whether atypical hyperplasia occurs in this species is not known.

A similar response to estrogen has been demonstrated in the rat by McEuen,[24] by Herold and Effkemann,[25] and others.[26] Again, these changes seem to stem from proliferation of undifferentiated cells.

Precancerous changes and true carcinoma have been induced in the mouse with similar experimental procedures.[27, 28, 29] These tumors are usually located in the vagina or on the posterior lip of the cervix. They are true carcinomas showing invasion, metastases, and transplantability. Gardner[30] is of the opinion that they are related solely to the experimental procedure and that hereditary factors have probably been eliminated. Inasmuch as the endocervix of the mouse does not resemble that of the human being in that there is no columnar

Fig. 2.—Cervix of pregnant women.
A, Reserve-cell proliferation.
B, Reserve-cell hyperplasia.
C, Adenomatous hyperplasia of reserve cells.
D, Atypical hyperplasias of reserve cells.

epithelium, the response in this species is not a proliferation of reserve cells, but an overgrowth of squamous epithelium. Such a response does occur but rarely in the pregnant woman (Fig. 5, *A*).

Wollner[31] noted striking metaplasia in the cervix of one castrated woman receiving estrone. He claimed disappearance of the metaplastic growths after cessation of the hormone therapy. After analyzing 170 patients with endometrial hyperplasia, Bainborough[32] thought that metaplasia of the endocervical epithelium occurred with greater frequency than in a random control series. Greene[33] could not confirm this.

In an effort to study the relationship of cervical epithelial changes in the human being to estrogen stimulation, and also to relate some of the animal experiments to human findings, the following experiment was planned.

Two groups of cervices were selected as controls. Ninety-two were chosen serially from current pathological files, excluding those showing carcinoma and twenty-three were taken from postmenopausal patients. Two hundred fifty-one cervical biopsies from women in approximately the twenty-eighth week of pregnancy were studied. Eighty-one cervices from newborn infants were selected. Fifteen menopausal or postmenopausal women received cervical biopsies and then were given 100,000 units of estrone sulfate daily for fourteen days by hypodermic injection of 150 mg. of stilbestrol by mouth daily for the same period, following which total hysterectomy was performed. These cervices were also included. Twenty-three cervices obtained from postmenopausal women suffering from endometrial hyperplasia also furnished part of the study. Cervices of five adolescent girls were reviewed. Finally, two cervices were obtained from patients with granulosa-cell tumors, and two from patients with theca-cell tumors.

The biopsy material from pregnant women was the same as used in the Johns Hopkins study,[2] while the newborn cervices were from our own previously reported paper.[3] In each instance these slides were reviewed again in the light of our increased knowledge concerning the role of the reserve cell. As a result the incidence of certain changes varies slightly from that previously reported.

In the menopausal and postmenopausal group of patients the age varied from 42 to 83 years. The majority fell in the older category and were no longer menstruating. The adolescent material was particularly difficult to obtain and history regarding menarche almost nonexistent. The ages varied from 7 to 14 years.

For comparative purposes photomicrographs depicting four phases of reserve-cell proliferation for the following groups of patients are presented on plates: (1) newborn infants; (2) pregnant women; (3) postmenopausal women with endometrial hyperplasia; (4) menopausal or postmenopausal women treated with natural or synthetic estrogens.

In each plate the photomicrograph labeled A shows the mildest type of reserve-cell proliferation. Here, these more or less cuboidal cells with large

Fig. 3.—Cervix of postmenopausal women with endometrial hyperplasia.
A, Reserve-cell proliferation.
B, Reserve-cell hyperplasia.
C, Adenomatous hyperplasia of reserve cells.
D, Atypical hyperplasia of reserve cells.

C, Adenomatous hyperplasia of reserve cells.
D, Atypical hyperplasia of reserve cells.

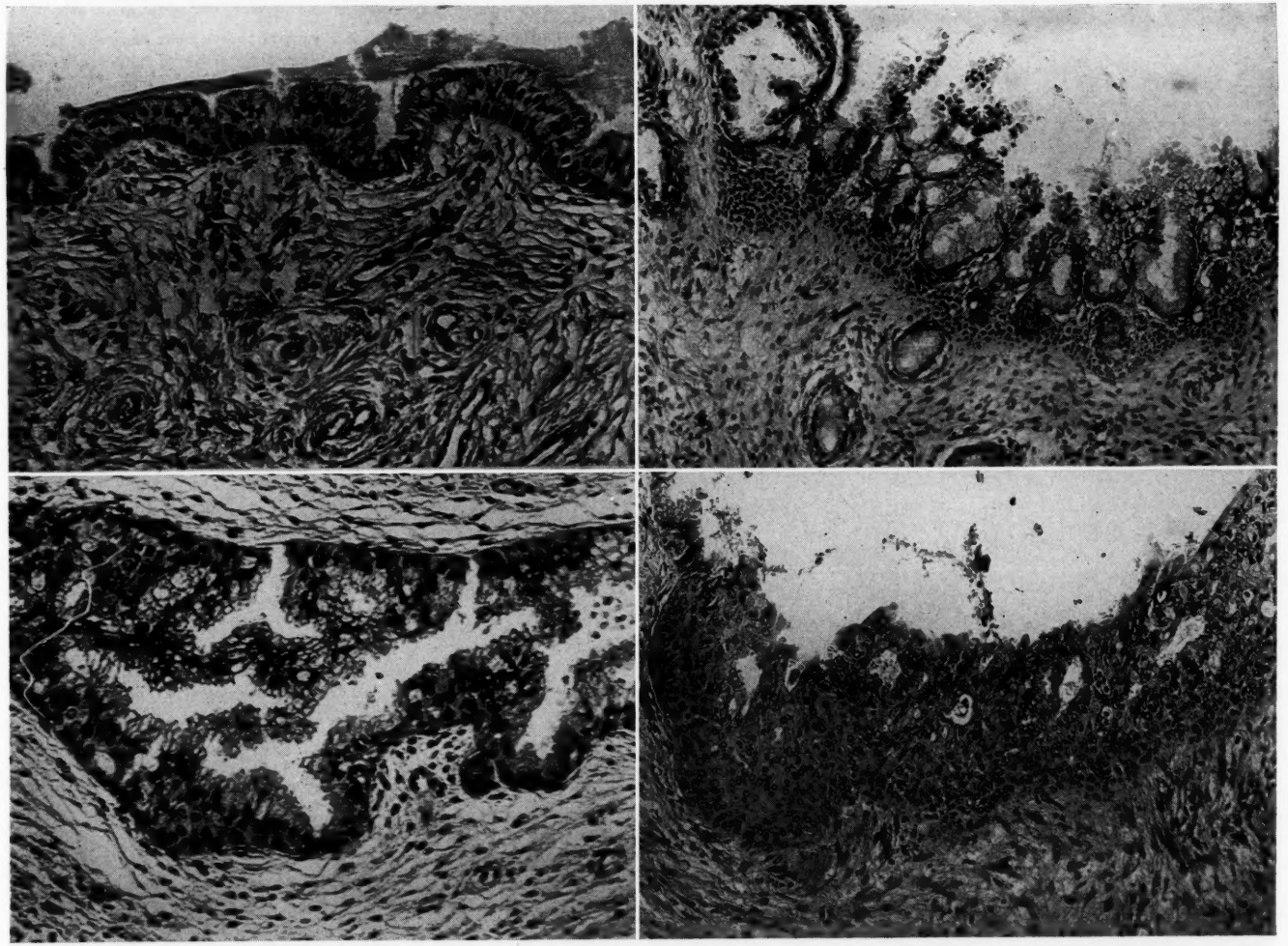

Fig. 4.—Cervix from menopausal or postmenopausal women treated with natural or synthetic estrogens.
A, Reserve-cell proliferation.
B, Reserve-cell hyperplasia.
C, Adenomatous hyperplasia of reserve cells.
D, Atypical hyperplasia of reserve cells.

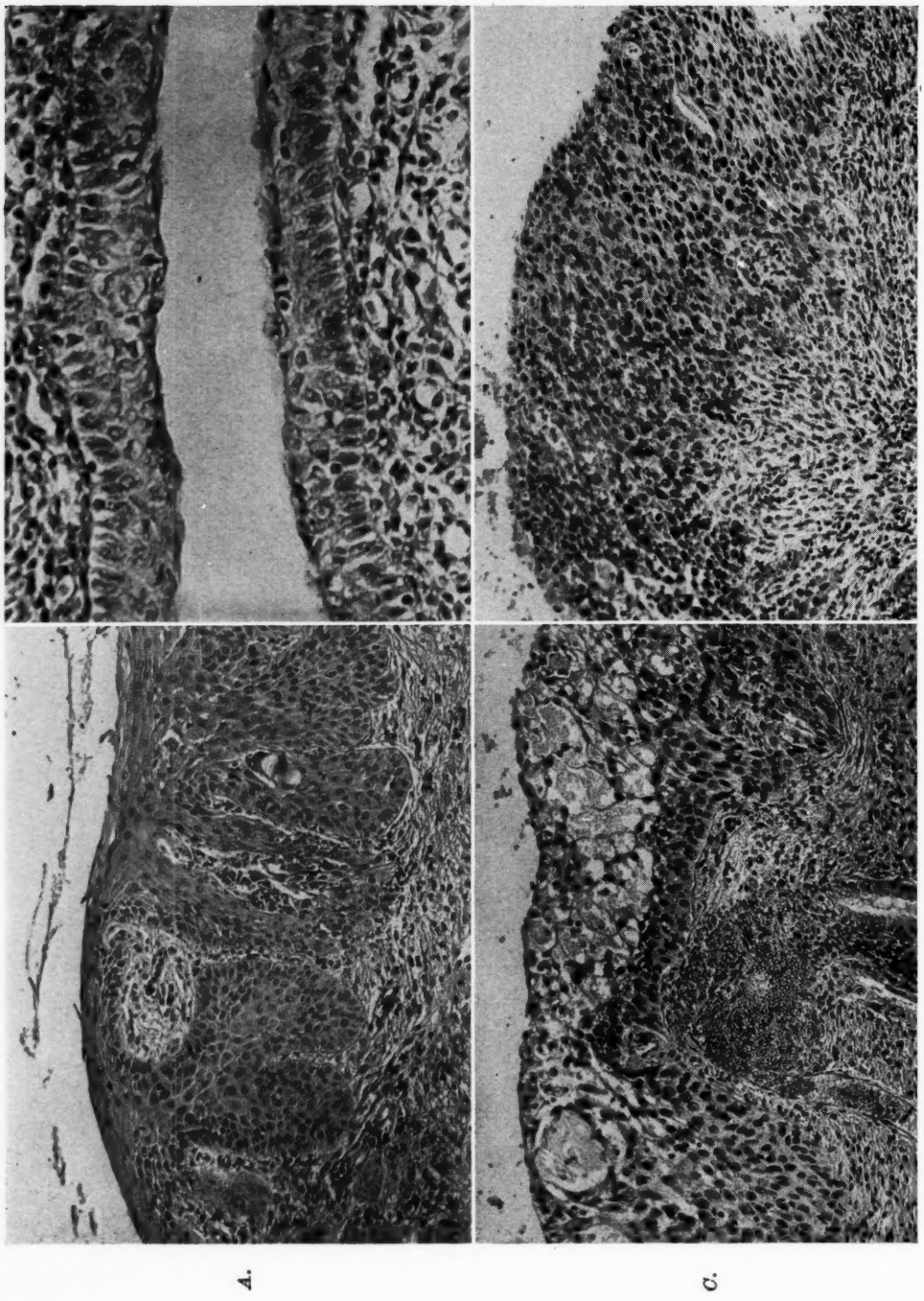

Fig. 5.—*A*, Cervix from a pregnant woman showing epithelial hyperplasia in pregnancy. *B*, Cervix from a 10-year-old girl showing reserve-cell proliferation. *C*, Cervix from a pregnant woman showing reserve-cell proliferation. *D*, Cervix from a pregnant woman showing marked atypical hyperplasia of reserve cells.

vesicular nuclei and rather scant cytoplasm appear in a single continuous line just above an inconstant basement membrane and below the columnar cells.

The photomicrographs labeled B show hyperplasia of these reserve cells. They are piled one on top of the other but the nuclei are in orderly arrangement and hyperchromatism is not present. In some of the photomicrographs there is a tendency to vacuole formation and also formation of squamous cells. The columnar cells are pushed out of the way by the rapidly proliferating reserve cells.

The illustrations labeled C show adenomatous hyperplasia of the reserve cells. Here new glands or glands within glands are formed. The derivation of these new glands from reserve cells seems quite evident.

Finally, the photomicrographs labeled D show atypical hyperplasia of the reserve cells. The nuclei are piled one on top of the other in disorderly arrangement. Especially in pregnancy, but also in the newborn infant there are hyperchromatism and atypism of the cells. Atypism is not so striking in the postmenopausal women treated with estrogen and rather insignificant in those with endometrial hyperplasia. The fact that these atypical changes are truly of reserve-cell origin is given weight by Fig. 5, *C* and *D*, which show contiguous sections from the cervix of a pregnant woman. *C* illustrates mild to severe reserve-cell hyperplasia. The particular vesiculation of the overlying epithelium is typical of reserve cells undergoing estrogen stimulation. As one follows this proliferation toward *D*, the hyperplasia becomes more and more marked and there develops an increasing irregularity of the cells, both as to polarity and staining characteristics. There appears, therefore, to be a gradual progression from reserve-cell hyperplasia to extreme atypical hyperplasia of these cells resembling carcinoma in situ. There is even some question in Fig. 5, *D* of invasion of these cells into the underlying stroma. It is these changes in pregnancy which are located within the canal, and which stem from the reserve cell which are sometimes reversible when the hormonal stimulation is terminated.

Fig. 5, *B* is from the cervix of a ten-year-old girl whose menstrual history is unknown. It is apparent that there is reserve-cell proliferation with a tendency toward squamous metaplasia. Of the five cervices available from girls of the ages 7 to 14, this was the only one to show any reserve-cell hyperplasia. Admittedly however, the material is insufficient for any interpretation.

Fig. 6, *A* shows a typical granulosa-cell tumor occurring in a patient 71 years of age. *B* demonstrates the accompanying cystic endometrial hyperplasia. Admittedly, however, the material is insufficient for any interpretation. plasia of the reserve cell similar to that shown in the foregoing figures.

The data from these various categories of patients are presented in tabular form in Table I. The two control series, namely, those chosen serially and those from postmenopausal women, are located in the first two columns of the chart. The control biopsies taken from menopausal and postmenopausal women prior to estrogen therapy are not included. This material was unsatisfactory due to lack of sufficient endocervical tissue. In two instances reserve cells were present. Those associated with endogenous estrogen appear

D, Cervix from a pregnant woman showing marked atypical hyperplasia of reserve cells.

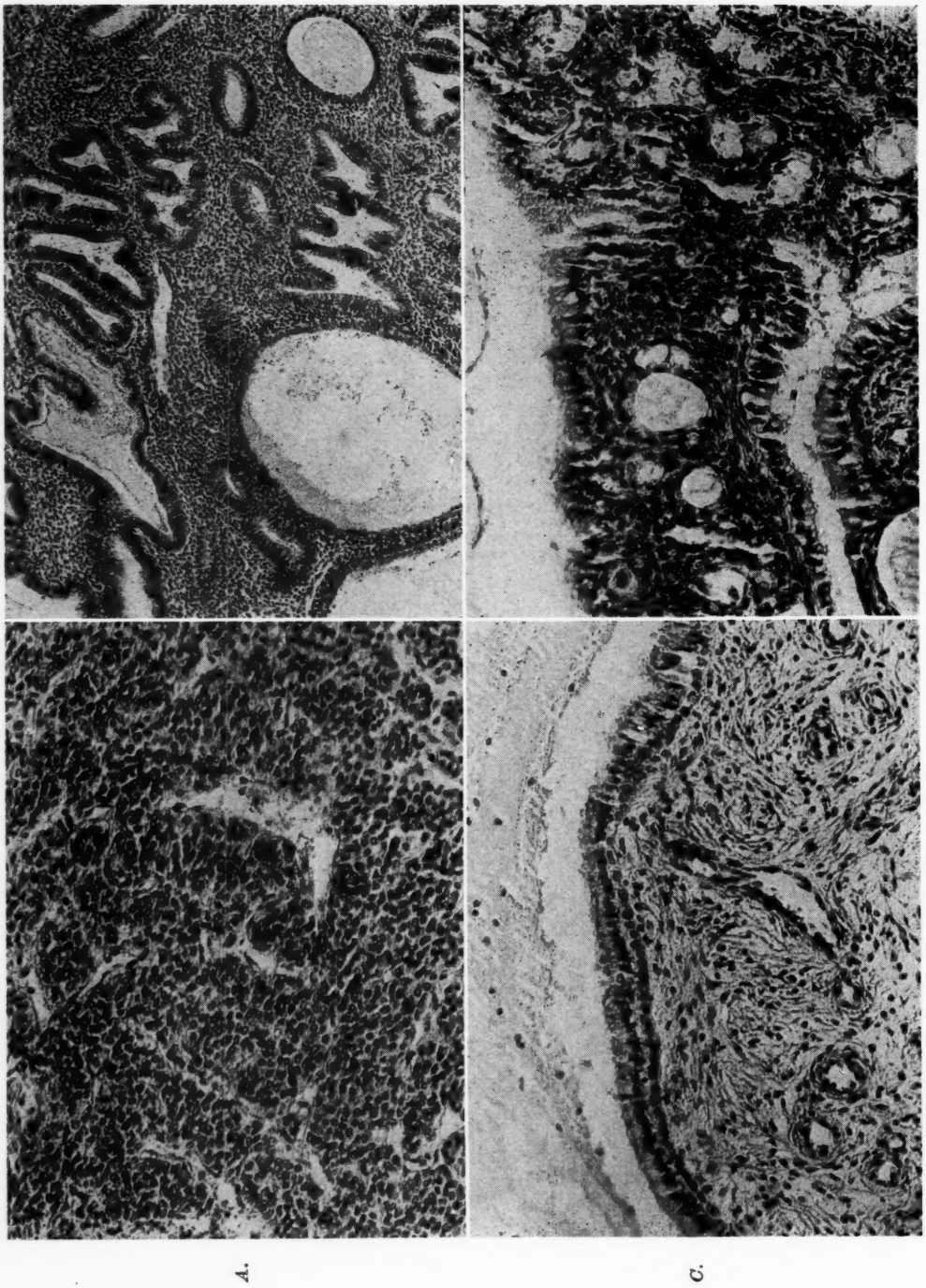

Fig. 6.—Effect of granulosa-cell tumor on the cervix.
A, Granulosa-cell tumor.
B, Accompanying endometrial hyperplasia.
C, Cervix showing reserve-cell proliferation.
D, Cervix showing adenomatous hyperplasia.

in the next three columns and those occasioned by exogenous estrogen in menopausal and postmenopausal women in the last column. It is readily apparent that while most of the changes studied occurred in normal and in menopausal women they are significantly increased during periods of endogenous or exogenous stimulation.

Table II is presented for statistical purposes to give some idea of the magnitude of this difference between the control series and those under estrogen stimulation. The two control series are grouped as are also those of the newborn, pregnant, and postmenopausal women with endometrial hyperplasia. In addition, the four separate changes which appear under estrogen stimulation are grouped. The increased incidence of the reserve-cell activity, namely, proliferation, hyperplasia, adenomatous hyperplasia, and atypism due to endogenous and exogenous estrogen is approximately three to four times that of the control series.*

There were four cervices from patients with feminizing ovarian tumors available for study. Two had granulosa-cell tumors and two theca-cell tumors. In all, typical reserve-cell proliferation was found. In no instance did this proliferation reach the extreme degree of atypism shown in some of the preceding cases.

TABLE I. THE INCIDENCE OF VARIOUS TYPES OF RESERVE-CELL ACTIVITY DUE TO ENDOGENOUS AND EXOGENOUS ESTROGEN

					ESTROGEN							
					ENDOGENOUS							
	SERIAL CONTROL 92		POST-MENO-PAUSAL CONTROL 23		NEWBORN 81		PREGNANT 251		POSTMENO-PAUSAL ENDOME-TRIAL HYPER-PLASIA 23		EXOGENOUS POST MENO-PAUSAL TREATED 15	
PATIENTS	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
Reserve Cell Changes.—												
Proliferation	28	30	1	30	73	90	138	55	23	100	15	100
Hyperplasia	21	23	4	17	42	52	113	45	17	74	15	100
Adenomatous hyperplasia	10	11	1	4	41	51	106	42	9	35	10	67
Atypical hyperplasia	0	0	0	0	4	5	36	14	1	4	2	13

It appears from this study that during periods when the estrogen level is naturally high or when estrogen is administered to patients during a time when there are no regularly occurring menstrual periods, there is a corresponding proliferation of reserve cells. In general, this is most marked when estrogen is given to menopausal or postmenopausal women. If estrogen is given to women who are still having some menstrual function the response is not striking. However, with advancing age the reserve-cell response to estrogen becomes more marked. This fact has been noted in some of the animal studies. Never, how-

*$\frac{\text{Difference}}{\text{Sigma}}$ of both endogenous and exogenous estrogen as compared to the control is in excess of 2.5.

TABLE II. TOTAL INCIDENCE OF RESERVE-CELL ACTIVITY DUE TO ENDOGENOUS AND EXOGENOUS ESTROGEN

PERCENTAGE			NUMBER*		
CONTROL	ENDOGENOUS	EXOGENOUS	CONTROL	ENDOGENOUS	EXOGENOUS
15.4	42.4	61.0	71/460	603/1420	42/60

*Positive observations/observations.

ever, in the small series here presented has any marked degree of atypism of reserve cells been shown in those patients treated with estrogen. On a theoretical basis such a response could be elicited just as it occurs in pregnancy if the proper dosage and proper duration of therapy were known. Neiburgs[34] has stated that if large doses of estrogen are given continuously the response of the cells becomes less and less marked and there is a tendency only to squamous metaplasia. In animals similar findings were noted and it is altogether probable that the most atypical responses occur quickly and at the beginning of therapy, and are probably not directly related to the dosage.

Neiburgs[35] and others too have postulated that there is some relationship between human cervical carcinoma and high levels of estrogen. Neither the animal work nor the data presented here can be taken to offer any evidence in support of this point. It is true that during pregnancy and perhaps during the newborn period there are changes in the reserve cell so markedly atypical that they resemble early carcinoma. Pund[18] has shown the derivation of carcinoma from these reserve cells, but to date there is no conclusive evidence that the changes herein demonstrated are in any way related to malignancy.

Conclusions

1. During pregnancy, the perinatal period, and the postmenopausal period in patients with endometrial hyperplasia there occur proliferation of the reserve cells of the cervix, hyperplasia of these cells, adenomatous hyperplasia, and atypical hyperplasia which seem to be related to the high levels of endogenous estrogen occurring in these patients.

2. Further evidence that estrogen may play some role in the production of these changes is the initiation of similar findings in cervices of menopausal and postmenopausal women treated with high doses of natural and synthetic estrogen for a short period of time.

3. A similar picture occurred in patients with feminizing tumors of the ovary.

4. These estrogen-induced charges show varying degrees of atypism which, as demonstrated in pregnancy, can be so marked as to be histologically indistinguishable from carcinoma in situ. However, there is no evidence, from this work, that they bear any direct relationship to human cervical carcinoma.

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Discussion

DR. EMIL NOVAK, Baltimore, Md.—Dr. Hellman's study is not of merely academic importance. It has obvious bearings on a good many problems other than the histologic changes in the cervix of pregnancy, such as the question of epidermization and the relations between estrogen-induced lesions and cancer—or, to broaden the statement, between the estrogen and cancer. I suspect that the work reported today is a sort of supplement to the interesting study made by Dr. Hellman and a group of collaborators in 1951, describing certain proliferative and metaplastic changes in the cervix of pregnancy. Incidentally, in rereading that paper, I was interested and somewhat amused to note that "reserve" cells or "basal" cells are not even mentioned, this being true also of the paper of Carrow and Greene on the same subject at almost the same time. And yet the study presented today revolves almost completely about these reserve cells.

This makes me raise the question as to whether Dr. Hellman has not recently become too enthusiastic about the role of these cells. They were well described by Carmichael and Jeaffreson in 1939, but have not seemed to make a great deal of impression upon pathologists. As a matter of fact, the term "reserve cells," and the much older one of "indifferent" cells, dating back to the early days of Carl Ruge and Robert Meyer, are used with different connotations by different authors. An excellent review of these differing viewpoints is given by Fluhmann in a paper which has just appeared in the current number of *Surgery, Gynecology and Obsterics.* It seems to me that Hellman's application of the reserve-cell concept to epidermization is far too inclusive, and I am old-fashioned enough to believe that many instances of this cervical change are explainable by "horizontal" growth of the squamous epithelium beneath the columnar epithelium, as originally described by Meyer in the "healing" stage of erosions.

Dr. Hellman's pictures seem to leave no doubt as to the responsiveness of the cervical reserve cells to hormonal stimulation. On the other hand he has shown the reversibility

of these changes, as might almost be assumed on the basis of previous experimental evidence. This seems to support the apparent reversibility of at least some of the cervical pregnancy changes reported in 1951. In retrospect, it would also seem that in this paper Hellman and his co-workers did not sufficiently emphasize the very low incidence of lesions which were really cancerlike, and I could mention instances in which pathologists, associating such suspicious lesions characteristically with pregnancy, have leaned too far backward and thus incorrectly interpreted genuine cancer as of this endocrine character.

The endometrium is the tissue which par excellence is under hormonal control, and hyperplasia is readily produced by excessive estrogen stimulation. And yet I have never been impressed with histologic evidence of estrogen-induced changes in the cervices of uteri showing hyperplasia of the endometrium. It is difficult to explain why no one has, so far as I know, produced endometrial carcinoma experimentally, while Gardner and others have repeatedly produced cervical cancer in mice by prolonged estrogen stimulation.

The whole question of the relation of estrogens to cancer development is a fascinating one, and one of its most important facets is the relation of the hormonal to the genetic factor in carcinogenesis. I myself have devoted a couple of papers to a review of this subject, which has stepped again into the forefront of cancer interest because of the work on "steroid patterns" being done at the Memorial Hospital, as reported recently by its director, Dr. Cornelius P. Rhodes.

DR. FRANK R. LOCK, Winston-Salem, N. C.—The persistence throughout life of incompletely differentiated cells in various tissues of the body poses a problem of both theoretical and practical interest to those concerned with the large group of diseases characterized by disturbances in the proliferation, differentiation, and organization of cells. Tardily emphasized by biologists and until recently practically ignored by pathologists and clinicians, this group of cells in all probability plays a major role in hyperplastic, metaplastic, and neoplastic growth. A few examples will suffice to emphasize this point.

It is well established that all tissues in the vicinity of blood vessels contain incompletely differentiated mesenchymal cells which persist throughout life, and which under both normal and abnormal conditions display their latent ability to differentiate into tissues of various types. The endometrial stroma is an excellent example of the persistence after birth of large masses of incompletely differentiated cells of embryonal type. Formerly histologists, when attempting to classify the connective tissues, have avoided a specific designation for the endometrial stroma, merely referring to it as a "peculiar type of connective tissue." In the recent literature, it is frankly stated that the endometrial stroma is a tissue which "resembles mesenchyme." It is not surprising, therefore, to see this tissue, under certain circumstances, express latent developmental potencies.

These potencies are expressed to the fullest degree in the group of tumors known as malignant mixed mesodermal tumors. In these neoplasms, groups of mesenchymal cells differentiating into loose connective tissue, cartilage, bone, fat, smooth muscle, striated muscle, and glandular epithelium have been encountered. It will be recalled that all of these structures are embryologically indigenous to the mesenchyme.

We are of the opinion that the so-called "reserve cells" under discussion here today belong to the broad group of incompletely differentiated cells possessing latent developmental potencies. These cells, however, represent a more advanced stage of differentiation than the cells previously alluded to, and their latent potency is expressed only in their ability to replace the normal cylindrical cells of the endocervix and to differentiate into squamous epithelium-like structures. The latter change is, of course, known as metaplasia.

The original concept of metaplasia as proposed by Virchow, namely, that there is a direct transformation of adult cells into cells of another type, is not supported by data. Pathologists in general are in agreement that the process of metaplasia is an indirect one whereby the substitution of one type of cell for another is accomplished by further differentiation of incompletely differentiated cells.

The term metaplasia, as it relates to the cervix, should then apply only to those instances in which there is further differentiation of the "reserve cells" of the endocervix, and possibly to the occasional instance in which there is transformation of the nonkeratinizing squamous epithelium of the portio vaginalis into true epidermis. Ingrowth of stratified squamous epithelium from the vaginal surface of the cervix into the endocervix is accomplished through *hyper*plasia—that is, the production of more cells of the same kind—and should not be referred to as *meta*plasia, since this process involves the differentiation of more kinds of cells.

The essayist has made a valuable contribution to this subject in that he has produced evidence as to the substance which enables the "reserve cells" of the endocervix to express their latent developmental potencies.

It is not surprising that a proliferation of the "reserve cells"—that is, hyperplasia—without further differentiation would produce a structure which in some instances is distinguishable only with difficulty from carcinoma. We believe that the basilar cylindrical cells of the stratified squamous epithelium of the portio vaginalis are capable of producing an identical picture. It is to be remembered that these too are incompletely differentiated cells which ordinarily differentiate into squamous cells, but which in rare instances differentiate into structures quite foreign to the cervix.

In the attempt to evaluate both of these types of proliferation as regards malignancy, it is our concept that immaturity of cells and evidence of activity as manifested by increased cellularity, basophilia, hyperchromatism, and mitosis are not adequate for the diagnosis of cancer. We feel that in addition to these changes the individual cells must show different degrees of anaplasia, a finding usually referred to as pleomorphism.

DR. RICHARD TE LINDE, Baltimore, Md.—There is a practical application of Dr. Hellman's work which has not been touched upon by the discussants today. Some of you may remember Fig. 5, *C* and *D*, I think, which looked to me like intraepithelial carcinoma. In fact, he tells me that I looked at that slide four or five years ago and called it intraepithelial carcinoma. The woman has remained well for five years. I still think in looking at that slide that I could do nothing else but label it intraepithelial carcinoma. The fact that she has remained well for five years does not absolutely prove that that woman is never going to have carcinoma of the cervix. In a retrospective study that we made on invasive cancer we found in one case that intraepithelial cancer had been present as long as 17 years in a biopsy and had been overlooked.

Now those are the things that make it hard, and I think one practical thing which comes up not infrequently is the finding of a biopsy such as that, or perhaps not quite as definite as that, perhaps only suspicious, during pregnancy. What is the clinician to do? Well, the diagnosis of intraepithelial carcinoma is practically never an emergency. You can watch that patient, and our routine has been to watch those patients through the pregnancy, perform a biopsy subsequently, and ultimately come to what we think is the proper diagnosis. On the other hand, we have terminated one pregnancy with an extremely malignant-looking intraepithelial cancer. It was at the very early part of pregnancy when the diagnosis was made; the woman had had several children, and felt we should go ahead with a hysterectomy. But that is the only pregnancy we have terminated to date for carcinoma in situ. Our general policy is not to do it.

On the other hand, what has happened to some of the people that have been watched with intraepithelial cancer? I have four cases that I would like to report to you very briefly, for I think they are very important and therefore I think they should be on record. The first case is that of a woman who had a biopsy during pregnancy and was found to have intraepithelial cancer. The people who performed the biopsy decided to do nothing, but let her have her baby. Ten months later she turned up in our clinic. We did a routine biopsy and found intraepithelial cancer. We knew nothing about the previous history. When that woman came to hysterectomy she had a great deal of intraepithelial cancer in the cervix, ten months after the cessation of her pregnancy.

Now the second case is even more interesting. A girl had a miscarriage at about three months. To complete it she was curetted, and there was one little bit of tissue which was accidentally obtained in the curettage. The pathologist sent it up to us, and we agreed with him that it was intraepithelial cancer; but it was such a tiny bit of tissue that we thought we'd watch her for a while. We had four or five smears made in the course of the next 11 months that we watched her. They were all positive. We took several biopsies; they were all negative. We did a conization, but could find no cancer in the tissue. Finally, after 11 months, another biopsy was taken, and there it was. We were about to operate on this woman when one of the housemen came to me and said, "This thing has extended to the vaginal vault. I did a Schiller test on her two days ago, took a biopsy from the vaginal vault, and here is intraepithelial cancer of the vaginal vault." We watched that woman too long, and that extension occurred within 11 months.

The third patient is a woman who had a biopsy in another hospital while she was pregnant. A cesarean section was done, and a subtotal hysterectomy. I think it was the intention of the man who operated on her to do a total hysterectomy, but for some reason—technical, I believe—it was not done. One year later this woman arrived in our clinic with a mass in the fornix. We biopsied that mass through the vaginal vault and found epidermoid carcinoma. The cervix still looked perfectly normal.

The fourth case is one that occurred at the Woman's Hospital in Baltimore. At the seventh month of pregnancy a biopsy was taken and intraepithelial cancer was diagnosed. A cesarean section as done; the uterus was left in. Six weeks after delivery this woman had a gross lesion on the cervix, and invasive cancer was diagnosed from biopsy.

Here are four cases, then. One remained intraepithelial ten months after the diagnosis was made. One case, the last one that I mentioned, eventually proved to be a Stage I cancer—an invasive cancer—as early as six weeks after delivery, and one of the other two eventually became a Stage II carcinoma.

We are cognizant of these changes which Dr. Hellman has described. One should not be in a hurry to make up his mind, but, on the other hand, one should not be too slow. We take these lesions seriously.

DR. WILLARD ALLEN, St. Louis, Mo.—The sections of the cervix shown by Dr. Hellman reminded me very much of sections which were obtained by myself and a few others about 1932, when we were studying the effects of the sex hormones, both estrogen and progesterone, on the vaginal mucosa of the mouse. The only reason for mentioning this is to point out that the vaginal epithelium—and I am sure also the cervical epithelium—really has considerable potentiality to drift in one way or another, depending upon the hormonal stimulus to which these epithelial cells are being subjected. The mucosa of the castrated or immature rat or mouse is very thin and contains a basal layer and another layer just outside, which may or may not contain mucin. That is the type of vaginal mucosa which is present in the rodent that was used for so many years for measuring estrogen. When estrogen is given to such animals the very thin atrophic mucosa, which really does not look like the atrophic mucosa of the human vagina, responds promptly and within 48 hours, as many of you know, becomes 10 to 15 cells thick, desquamating squamous-appearing epithelial cells which are cornified. During pregnancy in these rodents the vaginal mucous membrane is quite different, and unless one is experienced he would never recognize it as coming from the vagina. The mucosa in the pregnant animal is much thicker, does not contain glycogen like the human vaginal mucosa, but contains mucin. The basal or reserve layer contains no mucin. Under one circumstance—namely, stimulation by estrogen, whether by injection or from natural sources—this basal layer of cells develops into squamous epithelium. Under another circumstance—namely, pregnancy—the basal layer produces cells which contain mucin. At the end of pregnancy this thick layer of mucified cells is desquamated, and beneath it grows up, as estrogen reappears, a cornified layer of stratified epithelium which looks very much like the epi-

thelium that Dr. Hellman observed in these situations where estrogen, whether given to the patient or produced by the patient herself, was acting for some period of time.

In those days the exact cause of the mucous change in the vagina of the pregnant rodent remained a mystery for some time. It was unraveled only by virtue of the fact that progesterone itself had absolutely no effect on the vaginal mucosa of the castrated rodent. Hence the mucification which occurred during pregnancy was certainly not due specifically to the progesterone. However, it could not easily be produced by estrogen alone. When a combination of the two hormones was given, such as one might expect during pregnancy, beautiful mucification of the vagina was obtained.

I mention these studies on the vagina only to emphasize that what is seen in the cervix or vagina of an individual is probably dependent in most instances on what hormones are stimulating the epithelium. The most interesting part to me of Dr. Hellman's work is that he has been able to show that in the situations in which large amounts of estrogen are being produced this basal layer of epithelium, which presumably is the source of the mucus-producing cells of the normal cervix, tends to become stratified, resembling to a certain extent the vaginal epithelium of the woman.

DR. HELLMAN (Closing).—Dr. Novak and Dr. Te Linde have both been a source of stimulus to me, and I suspect that my original interest in these changes was due to some questions which Dr. Te Linde asked me shortly after the war.

This paper, as Dr. Novak indicated, is merely a continuation of work which has now been going on about seven years. I do not think he should be critical of the fact that we have added a new term, "reserve cell," a term which did not appear in the previous paper. I think that this merely represents an increase in my own knowledge of the subject with continued study of these changes, and I would not be surprised if, as we go along, our minds may again be changed. It is true that these cells were described a long time ago by Ruge and by Robert Meyer. I think their multipotentialities are only just beginning to be realized, as Dr. Lock indicated.

In regard to the cases that Dr. Te Linde mentioned, I can say only that in the present incomplete state of our knowledge regarding these changes we are faced with tremendous difficulty in determining whether they are truly malignant or are reversible. There is one point, I think, which is helpful, and that is that the commonly reversible lesions in pregnancy occur in the canal and not in the ectocervix. It seems to me that, if a lesion is high in the canal, one might hazard a guess that it would revert to normal.

As for Dr. Allen's comment on animals, I would like to say that, although it was common knowledge to him that a good deal of animal work had been done on this subject, I was amazed at its volume. Many of these publications are in journals which we clinical specialists do not ordinarily see. I also think that many of the people who originally worked on animals in an effort to produce carcinoma with hormones are now discouraged. As you know, no carcinoma of the cervix has ever been produced in any animal, with the exception of Dr. Gardner's mice. I have looked at those tumors, and all I can say is that they are different from cervical carcinomas in human patients.

THE TREATMENT OF URINARY INFECTIONS*

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PRIOR to 1936, when Rosenheim[1] introduced mandelic acid as a urinary antiseptic, there were few drugs of any appreciable value in the eradication of urinary infections. Many chemical compounds had been used for this purpose, and most of them had been found to exert bactericidal and bacteriostatic action against the common offending organisms of urinary tract infections when applied to cultures in vitro, but were of negligible value when used clinically. The history of these agents was reviewed by Walther[2] in 1937.

Soon after the introduction of mandelic acid the use of the sulfonamide drugs was extended to include the treatment of urological infections, and since that time the introduction first of newer and supposedly better sulfonamides and later of one antibiotic after another has been so rapid that one needs to pause and evaluate the results of the use of these agents in order to obtain a true picture of their value. In this study we believe that we are presenting an analysis of the results of treatment in a sufficiently large and varied group of urological infections to permit such an evaluation.

The material for this study has been obtained from a review of all urine cultures taken in our private offices for the three-year period Sept. 1, 1948, to Aug. 31, 1951. The period was selected because its beginning coincides with the beginning of our present method of obtaining and recording cultures, and its end permits at least a two-year follow-up of all patients studied. The treatment and observation of the patients are in no way limited to this three-year period. Many of the patients had been under treatment before Sept. 1, 1948, and a great many of them have been under either treatment or observation since.

During this three-year period, 1,916 urine cultures were taken. Of these 1,479 were positive and 437 negative.

Of the positive cultures 1,311 were obtained from 236 patients with some type of actual urinary infection. These patients have been divided for clinical analysis into seven groups as shown in Table I.

Of the positive cultures 168 were obtained from patients in whom the urine was microscopically negative, and there was no other evidence of urinary infection. In most of these patients the cultures were taken because of a history of urinary infection in the distant past, vague back or abdominal pains that might have been thought of as possibly urological in origin, or because the patients were referred for a search for focal infection. These patients re-

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ceived no treatment, and the positive cultures were considered as contaminants. In many instances, though not in all, this assumption was proved to be correct by subsequent sterile cultures. Another indication that many if not all of them were due to contamination is the wide difference between the incidence of the various organisms encountered in this group as compared with that in the group with actual infections. Such a comparison is shown in Table II.

TABLE I. CLASSIFICATION OF URINARY INFECTIONS

GROUP	TYPE OF INFECTION		NO. OF PATIENTS
I.	Acute cystitis, single attacks		68
II.	Acute cystitis, multiple attacks		65
III.	Chronic cystitis		22
IV.	Pyelonephritis		14
	Acute unilateral	4	
	Chronic unilateral	6	
	Chronic bilateral	4	
V.	Infection complicated by obstruction		44*
	Acute cystitis, single attack	3	
	Acute cystitis, recurring	15	
	Chronic cystitis	11	
	Pyelonephritis, acute, single	4	
	Pyelonephritis, acute, recurring	3	
	Pyelonephritis, chronic	16	
VI.	Infection complicated by calculus		15
VII.	Infection complicated by urethral lesions		8
	Total patients		236

*Pyelonephritis and cystitis occurred frequently in the same patient accounting for the greater number of diagnoses than patients in this group.

TABLE II. COMPARISON OF INCIDENCE OF BACTERIA OBTAINED IN CULTURES FROM REAL INFECTIONS AND FROM SUPPOSED CONTAMINATIONS

	GROUPS WITH NO. OF CASES IN EACH							TOTAL INFECTIONS	POSITIVE CULTURES SUPPOSEDLY DUE TO CONTAMINATION
ORGANISMS	I 65	II 65	III 22	IV 14	V 44	VI 15	VII 8	236	168 PATIENTS
Coli-aerogenes group	43	58	18	13	33	10	5	181	28
Staphylococcus albus	5	22	14	5	24	7	3	80	67
Staphylococcus aureus	5	6	5	1	2	1	1	21	12
Gamma streptococcus	8	7	4	5	9	2	3	38	34
Enterococci	4	6	6	1	8	1	1	27	10
Diphtheroids	5	14	6	3	8	–	1	37	48
Proteus	5	10	5	4	7	1	3	35	5
Alpha streptococcus	–	10	9	4	14	2	3	42	18
Anaerobic streptococcus	1	1	1	–	–	–	–	3	2
Beta streptococcus	–	3	3	–	4	–	–	10	–
Paracolon bacillus	–	5	–	1	3	1	–	10	1
Pseudomonas	1	–	2	–	–	1	–	4	1
Unidentified	5	–	–	–	–	–	–	5	
Multiple organisms in same or repeat cultures	12	53	14	1	33	1	8	122	42
Sensitivity done	5	11	6	0	5	1	3	31	

In addition to the types of organisms responsible for the infections, associated conditions, especially those of gynecological or urological nature which have been considered as having a possible etiological relationship to the infec-

tion, have been recorded. A very great variety of these have been encountered in occasional instances, but only those occurring with any significant frequency or seeming to have an especially significant etiological role have been tabulated. The incidence of these for the seven groups of infections may be seen in Table III. In most instances in which myomas were present the urinary infection occurred postoperatively. In the case of vaginal relaxation the urinary infection was preoperative and postoperative in about an equal number of cases. Chronic cervicitis, the most common associated lesion, was usually treated, sometimes in the course of vaginal plastic operations and in other instances by cauterization. We consider careful attention to these associated lesions an important adjunct to any chemotherapy of urinary infections.

TABLE III. ASSOCIATED GYNECOLOGIC OR UROLOGIC CONDITIONS CONSIDERED OF POSSIBLE ETIOLOGICAL SIGNIFICANCE

	GROUPS AND NO. OF PATIENTS							
TYPE OF CONDITION	I 65	II 65	IV 14	III 22	V 44	VI 15	VII 8	TOTAL
Cervicitis, chronic	18	12	4	2	5	–	1	42
Vaginal relaxation with cystocele, etc.	14	11	3	1	5	4	1	39
Relaxed vesical sphincter (stress incontinence)	7	4	3	–	2	–	–	16
Myomas of the uterus	6	5	2	1	3	1	3	21
Associated with vaginal plastic	8	6	1	–	3	1	1	20
Post hysterectomy	4	9	2	–	4	–	1	20
Trichomonas vaginitis	3	1	1	–	1	–	–	7
Carcinoma of cervix, treated	2	1	1	–	1	–	–	5
Carcinoma of endometrium, treated	2	1	1	–	–	–	–	4
Honeymoon	2	2	1	–	–	–	1	6
Superimposed on interstitial cystitis	2	1	–	–	–	–	–	3
Papilloma or papillary carcinoma of bladder	1	–	2	–	–	–	–	3
Nephroptosis	1	1	–	–	8	–	–	10
Neurological bladder	–	–	4	–	1	–	–	5

Group I: Acute Cystitis, Single Attacks; 68 Patients

The primary purpose in this study has been to evaluate the efficiency of the various therapeutic agents used in the treatment of urinary infections. This group seems particularly adaptable to this purpose as the infections for the most part have been uncomplicated by gross urological lesions. The results of treatment with the various drugs used is shown in Table IV.

Antibiotics were used only 4 times in this group. Chloromycetin was used 3 times successfully because of previously known sensitivity to sulfonamides. In 2 of these cases the offending organism was coli-aerogenes alone, and in the third coli-aerogenes with gamma streptococci. Aureomycin was used once for a heavy coli-aerogenes infection resistant to sulfonamides, with clinical cure, but with replacement of the coli-aerogenes by Proteus. The urine eventually became sterile without further medication.

Summary of Results in Group I.—

There was a symptomatic cure and the urine was rendered microscopically negative in all cases. Cultures remained positive after treatment as follows: *Staphylococcus albus* was cultured 5 times when the original cultures had shown

a different organism. The same was true of gamma streptococcus 4 times, of diphtheroids twice and of Enterococcus once. It is almost certain that these organisms were contaminants.

TABLE IV. RESULTS OF DRUG OR ANTIBIOTIC THERAPY IN GROUP I: 68 PATIENTS WITH SINGLE ATTACK OF ACUTE CYSTITIS

	SUCCESS	FAILURE	NEW ORGANISMS
A. Sulfadiazine.—			
Coli-aerogenes group alone	13	1	1
Coli-aerogenes group plus anaerobic streptococcus	1		
Gamma streptococcus	2		
Staphylococcus aureus	1		
Proteus	1		
Pseudomonas aeruginosa	1		
Diphtheroids	2		
Staphylococcus albus	1		
Unidentified	1		
B. Gantrisin.—			
Coli-aerogenes group alone	10		
Coli-aerogenes group with gamma streptococcus	1		
Gamma Enterococcus	1		
Micro-aerophilic gamma streptococcus	1		
Proteus	2		
Diphtheroids	1		
Staphylococcus aureus	1		
Unidentified	3		
C. Terfonyl.—			
Coli-aerogenes group alone	5		
Coli-aerogones group with anaerobic gamma streptococcus	1		
Coli-aerogenes group with gram-positive coccus	1		
Staphylococcus aureus	1	1	1
Escherichia coli with *Staphylococcus albus*	1		
Proteus with gamma streptococcus	1		
Diphtheroids	1		
Diphtheroids with *Staphylococcus albus*	1		
Unidentified	1		
D. Sulfathalidine.—			
Coli-aerogenes group alone	2		
Coli-aerogenes group with gamma streptococcus	2		
Coli-aerogenes group with anaerobic streptococcus	1		
Coli-aerogenes group with gamma Enterococcus	1		
Proteus with *Staphylococcus albus*	1		
Diphtheroids with *Staphylococcus albus*	1		

The persistence of coli-aerogenes and anaerobic streptococci in a patient successfully treated by resection and radon for papillomas of the bladder probably represents a real infection, although there was no pyuria and the patient was symptom free. One coli-aerogenes infection which failed to respond to sulfadiazine was successfully eradicated by Sulfathalidine.

The sensitivity of the organisms to antibiotics was tested 5 times, but in this group this test was of little value as the infections responded in almost every instance to the original drug used, usually a sulfonamide. The rapid cure and failure to recur of the infection in this group seems to render further urological study unnecessary. However, in 8 patients either retrograde or intravenous urography was done with normal findings.

The obtaining of sterile cultures by the use of Sulfathalidine when the original offending organism was other than a member of the coli-aerogenes

group makes us wonder if these organisms were not contaminants. In a previous study one of us[3] found that the effectiveness of this drug was largely limited to *Escherichia coli.*

Group II: Acute Cystitis, Multiple Attacks; 65 Patients

The incidence of the various organisms responsible for the infections in this group may be seen by reference to Table II. It will be seen that the coli-aerogenes group is again as in all groups greatly in the majority. Mixed organisms occurred in the same cultures 21 times, and the organisms were different in at least some of the different attacks 32 times. As all organisms grown are tabulated, the number of organisms listed under Group II in Table II is greatly in excess of the 65 patients in this group. This is true of all groups.

The clinical significance of an occasional attack of cystitis at long intervals is thought to be little more suggestive of organic urological pathology than is a single attack. On the other hand, we believe that many attacks occurring at short intervals are suggestive of organic disease and should lead to more thorough investigation. Accordingly, we have divided the patients in this group into four subgroups according to the number and frequency of attacks. This division is shown in Table V which also shows the number and results of pyelographic studies.

TABLE V. DIVISION OF PATIENTS ACCORDING TO NUMBER AND FREQUENCY OF ATTACKS WITH NUMBER AND RESULTS OF PYELOGRAPHIC STUDIES

	NO. OF PATIENTS	NO. OF PYELOGRAMS	PYELOGRAM NORMAL
Less than 6 attacks Average interval more than 6 months	44	16	15
Less than 6 attacks Average interval less than 6 months	10	2	2
More than 5 attacks Average interval more than 6 months	5	4	4
More than 5 attacks Average interval less than 6 months	2	1	1
Unclassified	4	0	0

The results of drug therapy are shown in Table VI. As the individual attacks were always relieved the recorded failures indicate that some other drug had to be substituted in order to effect a cure.

It will be observed that, as in Group I, the sulfonamides were on the whole successful but that they did fail in 16 instances. It was largely for these failures or because of the development of sensitivity to sulfonamides that antibiotics were used in 18 cases. In all but one instance these were successful. Sensitivity of the organisms to the various antibiotics was tested 11 times, and the selection of the antibiotic to be used thereby determined. There were 4 instances of drug sensitivity, one of mild asthma from sulfadiazine easily controlled by Pyribenzamine, one of fever to 101° F., and vulval herpes from sulfadiazine previously used successfully in several attacks, one of slight fever from Terfonyl, and one of skin rash from Sulfathalidine.

Sulfathalidine was used more frequently in this group as we have found in previous studies that in *E. coli* infection it and Sulfasuxidine[4] are likely to protect patients longer against recurrent attacks than are the other sulfonamides.

TABLE VI. RESULTS OF THERAPY IN GROUP II

DRUG	TIMES USED	SUCCESS	FAILURE
Sulfadiazine	34	29	5
Sulfathalidine	22	16	6
Gantrisin	17	14	3
Terfonyl	12	12	2
Sulfasuxidine	2	2	0
Sulfamerazine	1	1	0
Chloromycetin	7	6	1
Aureomycin	6	6	0
Terramycin	2	2	0
Streptomycin	2	2	0
Penicillin	1	1	0
Mandelamine	2	2	0
Calcium mandelate	1	1	0

Group III: Chronic Cystitis; 22 Patients

This is a small group and the results of treatment on the whole have been disappointing. The bacteriology may again be seen by reference to Table II. The results of drug therapy may be seen in Table VII.

TABLE VII. RESULTS OF DRUG THERAPY IN CHRONIC CYSTITIS

DRUG	TIMES USED	SUCCESS	FAILURE
Sulfathalidine	9	2	7
Gantrisin	6	1	5
Sulfadiazine	5	1	4
Terfonyl	2	1	1
Sulfanilamide	1	0	1
Calcium mandelate	5	2	3
Mandelamine	2	0	2
Chloromycetin	4	1	3
Penicillin	4	1	3
Streptomycin	4	1	3
Terramycin	3	2	1
Aureomycin	1	1	0
Total	46	13	33

We ourselves were rather astonished to find that studies of the upper urinary tracts had been done in only 6 of these patients, for it is in conditions of this type that we feel that such studies are imperative. In the 6 studied, however, the upper tracts were normal. The chronicity and resistance to treatment are accounted for at least in some of the patients by associated conditions. By reference to Table III it will be seen that in this group there were 4 patients with neurological bladder, 2 with papillary carcinoma of the bladder, and one each who had beeen treated for cervical or endometrial carcinoma.

Although the failures for the individual drugs predominate, eventually by the use of different drugs 13 cures were effected. The antibiotics have proved more useful and important in this than in the preceding groups. Antibiotic sensitivity was determined only 6 times. It is apparent that we have

not used this important test as frequently as we should, but it is relatively new and was not available at the time that many of these patients were being treated.

Group IV: Pyelonephritis; 14 Patients

This small group consists of 14 cases of pyelonephritis uncomplicated by such conditions as obstruction or calculus. Four of them were acute unilateral, 6 chronic unilateral, and 4 chronic bilateral. Pyelograms were obtained in all but one case of the acute unilateral variety which responded promptly to treatment. In 2 of the chronic unilateral variety and one of the chronic bilateral type the pyelograms revealed abnormalities but not obstruction. In one there was an ectopic pelvic kidney. In another a functionless infected kidney without apparent obstruction. In 2 cases nephrectomy was performed for severe unilateral disease.

The results of drug therapy are shown in Table VIII.

TABLE VIII. RESULTS OF DRUG THERAPY IN UNCOMPLICATED PYELONEPHRITIS

DRUG	TIMES USED	SUCCESS	FAILURE
Sulfathalidine	6	4	2
Sulfadiazine	4	3	1
Terfonyl	4	3	1
Gantrisin	3	2	1
Chloromycetin	3	2	1
Streptomycin	2	2	0
Terramycin	2	1	1
Aureomycin	2	0	2

Group V: Infection Complicated by Obstructive Lesions; 44 Patients

This constitutes a complex group. As will be seen by reference to Table I, all types of infection encountered in the previous groups are represented in this group. The additional factor in each of these cases has been the obstructive lesions which it has been necessary to treat if hope for relief of the infection was to be entertained. The causes or types of obstruction were as given in Table IX.

TABLE IX. CAUSES OR TYPES OF OBSTRUCTION

Hydronephrosis due to:	
Ureteral stricture	27
Ptosis of kidney	8
Ureteropelvic junction obstruction from	
Stenosis	2
Aberrant vessel	1
Cause undetermined	3
Cause undetermined	2
Urethral stricture	3
Diverticulum of ureter	1
Polycystic kidneys	2
Total	49

Multiple obstructions were present in 5 patients.

The treatment for the obstructive lesions was as follows:

Ureteral dilatations	23
Urethral dilatations	3
Nephrectomy	3
Nephropexy with release of aberrant vessel	1
Nephropexy	1
Conservative treatment for nephroptosis	3

In 11 patients the infection was relieved by treatment of the obstruction without benefit of drug therapy. In former years before the advent of modern chemotherapeutic agents this was a common experience. The result of all treatment for the whole group was relief of infection in 32, failure in 12. The specific drug therapy with results is recorded in Table X.

TABLE X. RESULTS OF DRUG THERAPY IN INFECTIONS COMPLICATED BY OBSTRUCTIVE LESIONS

DRUG	TIMES USED	SUCCESS	FAILURE
Sulfathalidine	18	12	6
Sulfadiazine	15	13	2
Gantrisin	10	6	4
Terfonyl	9	6	3
Mandelate	6	2	4
Sulfasuxidine	1	1	–
Aureomycin	6	3	3
Streptomycin	5	3	2
Chloromycetin	4	2	2
Terramycin	3	3	–
Penicillin	1	–	1

Sensitivity tests were done in only 5 cases. There were two instances of mild drug sensitivity, one to Sulfathalidine and one to Gantrisin.

Group VI: Infection Complicated by Calculus; 15 Patients

This is a small group and not adequately representative of our calculus patients. Many of these patients are admitted, studied, and treated entirely in the hospital so that there are no cultures obtained in the office. The bacteriology again may be seen in Table II. Another indication that this group is not adequately representative is that Proteus was the offending organism in only one case. It is well known that this organism is very frequently involved in calculus disease.

The distribution of the calculi and the types of infection are shown in Tables XI and XII.

TABLE XI. DISTRIBUTION OF CALCULI

Renal, unilateral	9
Renal, bilateral	2
Ureteral, unilateral	4
Ureteral, bilateral	1

TABLE XII. TYPES OF INFECTION

Cystitis	5
Pyelonephritis	9
Pyonephrosis	2

One patient had both renal and ureteral calculi.

The types of surgical or instrumental therapy with results are shown in Table XIII.

TABLE XIII. TYPES OF SURGICAL OR UROLOGICAL TREATMENT OF CALCULI WITH RESULTS REGARDING INFECTION

TREATMENT	NO. OF CASES	SUCCESS	FAILURE
Nephrectomy	4	4	0
Nephroureterectomy	1	1	0
Nephrolithotomy	3	1	2
Ureterolithotomy	1	0	1
Cystoscopic removal of stone	1	0	1
Ureteral dilatations only	2	0	2
Stone passed	3	2	1

As can be seen from Table XIV the results of medication in this group were on the whole disappointing. Where the sole focus of infection consisting of the calculus-bearing infected kidney was removed the results were excellent. Where the stones even though small remained or were removed by conservative but somewhat traumatizing procedures the infection persisted in spite of medication.

TABLE XIV. RESULTS OF MEDICATION ON INFECTION

DRUG	TIMES USED	SUCCESS	FAILURE
Sulfadiazine	6	2	4
Sulfathalidine	5	0	5
Gantrisin	3	2	1
Terfonyl	1	1	0
Mandelate	3	0	3
Streptomycin	3	2	1
Aureomycin	2	0	2
Chloromycetin	2	0	2

Group VII: Infections Complicated by Urethral Lesions; 8 Patients

This is again a small and insignificant group. One of us (H. S. E.) in collaboration with our associate Dr. C. B. Brack[5] has recently reported in more detail on the significance of urethral lesions in the maintenance of urinary infection. The lesions encountered in this group were urethral polyps which were resected in 3 patients, a urethral valve causing partial obstruction and which was resected in one, one case of senile contracture, and 5 in whom there was chronic granular urethritis. Medication was carried out in conjunction with and following appropriate treatment of these lesions in all cases. The results of drug therapy are shown in Table XV.

TABLE XV. RESULTS OF MEDICATION IN INFECTIONS COMPLICATED BY URETHRAL LESIONS

DRUG	TIMES USED	SUCCESS	FAILURE
Sulfadiazine	5	4	1
Gantrisin	5	3	2
Terfonyl	2	1	1
Sulfathalidine	1	0	1
Mendelate	1	1	0
Terramycin	1	1	0
Streptomycin	1	1	0
Aureomycin	1	1	0

This group is too small to permit of sound conclusions, but we have recently become increasingly convinced of the importance of urethral lesions in the maintenance of persistent urinary infections in female patients. This has

come from the more frequent use of the McCarthy panendoscope in examination of the female urethra. We are of the opinion that some of the more resistant infections, particularly those in Groups II and III, may have been associated with and maintained by such lesions.

Comment

It should be concluded from the foregoing data that the preferred agents for the initial treatment of urinary infection of all varieties should be one of the sulfonamide drugs. These drugs have several advantages over the antibiotics as follows:

1. They are effective against a greater variety of organisms.
2. They are attended by fewer unpleasant side effects than most of the antibiotics, especially those administered orally. We have encountered only 11 instances of drug sensitivity to sulfonamides, 8 to sulfadiazine, and one each to Terfonyl, Gantrisin, and Sulfathalidine. All but one of these reactions were mild, consisting of skin rash, slight diarrhea, or slight nausea and vomiting. One patient who had taken sulfadiazine successfully several times before eventually developed a febrile reaction to the drug.
3. An antibiotic is likely to be entirely ineffective if used before the culture is reported. Each of the antibiotics is completely ineffective against some of the organisms that cause urinary infection.
4. The sulfonamides are cheaper.

The choice of sulfonamides has been more or less arbitrary and depended to some extent upon the preference of the one of the three of us, the two authors and our associate, Dr. C. B. Brack, who has been responsible for the treatment of the patient. Each of them has certain advantages and disadvantages as follows:

Sulfadiazine for acute uncomplicated infections is effective in relatively small doses, 2 Gm. daily for five to seven days. With this dosage there is little danger of crystalluria, but even so fluids should be forced and the urine kept alkaline during the administration of the drug. With the more severe and complicated infections 4 Gm. should be given daily, and with this dosage the previously mentioned precautions against crystalluria are even more important.

Terfonyl, a triple sulfonamide consisting of 0.5 Gm. tablets composed of equal proportions of sulfadiazine, sulfamerazine, and Sulfamethazine, is equally as effective as sulfadiazine and should be used in essentially the same dosage. The danger of crystalluria is only one-third as great as the solubility is dependent on that of each of the three component substances. The therapeutic effect, however, is that of the total sulfonamide concentration.

Gantrisin is highly soluble and therefore avoids the dangers of crystalluria. The required effective dosage, however, is greater, at least 4 Gm. daily for the simpler infections and 6 to 8 Gm. daily for the more complicated infections. The larger doses sometimes produce gastrointestinal disturbances. It has been claimed that the drug is more effective than the other sulfonamides

against some of the more resistant organisms, especially Proteus. Our results would not indicate that this is the case. In the simpler types of infection such as acute cystitis we have not found Proteus a particularly resistant organism. We have successfully eradicated this organism 11 times with sulfadiazine, 8 times with Gantrisin, 6 times with Terfonyl, and twice with Sulfathalidine. Proteus appeared in the cultures seven times following aureomycin for an originally different organism.

Although in this study Sulfathalidine has appeared to be successful a few times in eradicating organisms other than the coli-aerogenes group, we know from a previous study[3] that its effectiveness is largely against the *Escherichia coli* member of this group. The dosage is 4 Gm. daily and it is especially useful in the frequently recurring or chronic cases due to *E. coli*. In some of the most resistant and chronic cases it has been employed a week out of each month in an attempt to prevent recurrence. It is usually well tolerated, and this regime has often proved effective in previously troublesome cases.

The antibiotics are more likely to lead to sensitivity on the part of the patient and to the development of resistance on the part of the offending organisms than are the sulfonamides. It is our considered opinion, therefore, that the promiscuous use of antibiotics for minor infections such as colds or acute cystitis is an unwise practice. A patient may thus be rendered sensitive to an antibiotic which at a later date might be desperately needed for a more serious infection.

In this whole group of patients Chloromycetin was used 23 times. We have been particularly fortunate in that none of the patients developed serious blood dyscrasias as have been reported resulting from this antibiotic. Since the reports of such cases began to appear, we have limited the use of this antibiotic to severe infections in which the sensitivity test showed that it had the possibility of being the most effective therapeutic agent. Repeat courses should be avoided in as far as possible, as most of the reports of blood dyscrasias have shown them to result from repetition of the drug. When Chloromycetin is to be used the patient should be hospitalized and subjected to frequent blood studies.

The dosage of the various antibiotics has usually been 250 mg. four times daily for aureomycin and Terramycin, 500 mg. four times daily orally for

TABLE XVI. CHOICE OF ANTIBIOTIC IN BACTERIAL INFECTIONS IN THE FEMALE

KEY: I = first choice
II = second choice
– = ineffective

ORGANISM	PENICILLIN G	STREPTOMYCIN	AUREOMYCIN, TERRAMYCIN	CHLOROMYCETIN
Escherichia coli	–	II	I	I
Aerobacter aerogenes	–	II	I	I
Proteus vulgaris	–	II	–	I
Pseudomonas aeruginosa	–	I	–	I
Alpha and gamma streptococcus, Enterococcus	II	–	I	–
Staphylococcus albus and *aureus* and beta streptococcus	I	–	II	–

Chloromycetin, and intramuscularly for streptomycin, and for penicillin 300,000 units of procaine penicillin G twice daily, or 200,000 units of an oral preparation three times daily.

While in a general way the selection of an antibiotic to be used in a particular infection may be made according to Table XVI, a more efficient method which we highly recommend is to select an antibiotic in each case only after determining the sensitivity of the offending organism to the various antibiotics by the disk sensitivity test.

DISK SENSITIVITY TEST—TECHNIQUE OF BONDI, SPAULDING, SMITH, AND DIETZ[6]

1. Streak a blood agar plate with the organism. Distribute the inoculum evenly so as to obtain confluent growth.
2. Dip a sterile filter paper disk (0.7 mm.) in an appropriate dilution of the antibiotic.
3. Place the saturated disk in the center of the surface of one-fourth of the inoculated agar plate.
4. Repeat this procedure with the other antibiotics to be tested.
5. Incubate the plate for 18 hours and examine for areas of inhibition surrounding the antibiotic disks.
6. Results are interpreted as follows:

Less than 10 mm. inhibition	resistant
10-14 inhibition	slightly sensitive
15-19 mm. inhibition	moderately sensitive
20-30 mm. inhibition	very sensitive
Over 30 mm. inhibition	extremely sensitive

Note: Dehydrated disks impregnated with various antibiotics are available from several commercial sources.

CONCENTRATION OF ANTIBIOTICS USED FOR SENSITIVITY TESTS

Penicillin	50 units
Streptomycin	500 μg
Chloromycetin	500 μg
Aureomycin	1,000 μg
Terramycin	1,000 μg

Conclusions

From the foregoing data we believe that the following conclusions may be recorded:

1. The commonest form of urinary infection encountered in gynecological patients is acute cystitis.

2. Acute cystitis in a single attack or in several attacks at long intervals probably does not indicate organic urological disease.

3. Frequently recurring attacks of acute cystitis or chronic cystitis should lead to complete urological investigation.

4. The simple forms of urinary infection can usually be successfully treated by sulfonamide therapy.

5. Antibiotic therapy should be reserved for the more complicated and serious infections or those that have proved resistant to sulfonamide therapy.

6. Antibiotic therapy is likely to prove more effective if the antibiotic is selected by means of sensitivity tests performed on the offending organism for each individual case.

We wish to express our appreciation to Mrs. Isabelle G. Schaub for her helpful suggestions regarding the bacteriological phases of this study.

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Discussion

Dr. W. O. JOHNSON, Louisville, Ky.—The three-year study of urinary cultures taken in office practice, the treatment, and follow-up by Dr. Everett and his associates are quite conclusive and will aid in a proper evaluation of future therapy of such infections.

I wish, however, to ask some questions: (1) Did the patients have any side effects after the use of antibiotics, especially vaginal disturbances? (2) How does he explain the increased frequency of postoperative cystitis in cases of myomas? (3) In chronic cystitis with relaxation and residual infected urine, what are their procedures in clearing this infection before operation and their postoperative care of the bladder? (4) If over 68 per cent of the cases respond to sulfonamides and in only 18 cases of failure was antibiotic therapy used, was it necessary to have an average of over 4 cultures taken from each patient?

In our experience the avoidance of urinary retention after operation is the best preventive management of infection. Assurance of the ability to empty the bladder completely before discharge from the hospital is of paramount importance.

We know that the coli-aerogenes group is the cause of over 65 per cent of the genitourinary infections, and this organism responds most satisfactorily to triple sulfonamide therapy. In Dr. Everett's series there were only 16 failures out of 268 cases, and practically all were first treated with sulfonamide compounds. Why were they not grouped and compared?

We feel that such cases should not be treated with antibiotics until they have failed with a sulfonamide or become resistant, and then only the antibiotics should be used that have been tested for sensitivity. When antibiotic therapy is administered the patient should be taken into the hospital.

Our experience is for the most part limited to the use of Gantrisin, 4 grams daily when tolerated, and double the dose in chronic cases. It does not crystallize, is tolerated well, and has fewer side effects. If after forty-eight hours of treatment the case does not show response, the organism is tested for sensitivity, and the antibiotic best suited is added, such as Terramycin or streptomycin.

The authors have found that Sulfathalidine in *E. coli* infections gives excellent results and seems to protect the patients longer against recurrent attacks than the other sulfonamides.

In pyelitis, pyelonephritis, and with renal calculi or with obstruction and growths, successful treatment can be obtained only by removing the obstruction and then treating the infection as indicated. This should be done in the hospital and is not always successful.

I would have liked the author to show that his therapy was governed by culture findings. I feel that it would have been more conclusive.

DR. HOWARD C. STEARNS, Portland, Ore.—In the presentation we have just heard, Dr. Everett and Dr. Long have presented material that is most needed in the management of urinary tract infections. Such studies help us all to attack such infections in the most direct way rather than to apply more or less empiric methods so common in recent times.

Culture and isolation of bacteria are not new. Proper therapy, however, is distinctly new and surprisingly effective. One cannot fail to be amazed at the progress made in the last few years with such problems. As a matter of interest I turned to my lecture notes taken on urological infections in my student days in 1926. The professor was able, prominent, and abreast of the times. He considered the presence of bacteria in the urine to be not abnormal,

save for a few strains that were known to cause trouble. Most were present because the kidney "excreted them from the general bloodstream." With the exception of methenamine none of the numerous antiseptics he advocated is heard of today.

Antibiotics and chemotherapy have changed a former frequently insoluble problem into one solved with little difficulty. There is very little in Dr. Everett's message with which I could disagree. Certainly, to know the offending organism is basically important. Thereafter, to use the drug most effective against that organism follows as a simple truth. One must emphasize, however, the author's advice to seek out and to correct any such basic factors as ureteral and urethral obstruction, cystocele, focal infection, stones, etc., which may be behind repeated urinary infections. I have witnessed too much reliance on magic drugs by some who have overlooked such common physical factors responsible for infection.

The well-tabulated findings of Drs. Everett and Long certainly bear out my general experience and thoughts on this subject. By inquiry among my friends in urology and gynecology I find general agreement with the material presented. I would agree that sulfonamides are the most useful drugs in urinary infections. Therein lies a point I would like to direct to Dr. Everett. Most of our urological infections are those of acute urinary cystitis. Virtually all of these clear readily with sulfonamide therapy. Cultures require time and a bit of expense. After determining to our satisfaction that the patient can tolerate sulfonamide therapy, is it unwise to proceed directly with such therapy without recourse to identifying the offending organism? I am thinking of the busy office practice, the physician working in an isolated area, and so on. I must admit that I proceed on that basis very commonly, but never do so on our hospital teaching service. I may begin such therapy after a culture has been started, then change therapy if culture and clinical results indicate that use of another agent is necessary. Is such a policy unwise?

As Dr. Everett points out, certain antibiotics take precedence in treatment of certain infections. However, if the sulfonamides may also do the work well, is it not wiser to use them? Antibiotics are potent and valuable. They should be used in all the fields of medicine more sparingly and with more caution than has been a general practice. What a tragedy exists if a serious infection demands the use of penicillin or streptomycin and we find the patient to have been sensitized to such agents by their previous indiscriminate use in minor infections. Again, we must emphasize the fact that if any of these drugs is to be used, then by all means use it in adequate amount and over a sufficient period of time to effect a possible cure. Otherwise a strain of bacteria may become resistant and defy further therapy.

Prophylaxis against urological infections is now an important aspect of pelvic surgery. Prior to the advent of sulfonamides and antibiotics urological infections in vaginal plastic surgery were almost to be expected. Now they can easily be prevented by use of a proper antiseptic routinely given during the healing of the bladder postoperatively.

DR. JOHN HERMAN LONG, Baltimore, Md.—I want to apologize for the few sensitivity tests we have in the paper—the main reason being, as Dr. Everett pointed out, the difficulty of obtaining tests when we first started this study. It has been only in the last six years that a cheap and rapid method has been devised to test the sensitivity of organisms to the different antibiotics. We use the *disk* sensitivity test of Bondi and Spaulding, published in 1947. Various antibiotics are impregnated into the disks, and sensitvity of the organism is determined by its growth near by.

We routinely now test the organisms to the antibiotics. We do institute therapy immediately, usually with one of the sulfonamide drugs.

DR. EVERETT (Closing).—The reason for this study is that I am constantly seeing patients with symptoms and signs of urinary infection who have been treated with an antibiotic—all too frequently, penicillin. Perhaps 80 per cent of urinary infections are of the coli-aerogenes group, and the patients might as well be getting sterile water as penicillin. Such treatment is a waste of time and money.

Dr. Johnson asked one or two questions: Why the large incidence of postoperative cystitis following myomas? It is true that the 21 cases in which cystitis followed myomec-

tomy comprise a fair percentage of this group of infections, but they make up a minimal percentage of the myomas that we treat. He asked about the clearing up of infections in patients with relaxation before operation. Usually, if there is much cystocele and prolapse—which is the type that is likely to have a preoperative infection—we temporarily use a pessary and treat the patient with sulfonamides, or if the sulfonamides are ineffective, with the appropriate antibiotic.

About the average of four cultures per patient: It will be noted that 65 patients had multiple attacks of cystitis. We never treat a patient for cystitis or any type of urinary infection without a culture. Some of these patients with multiple attacks had not four attacks, but a dozen or more attacks, and that accounts for the number of cultures. Also, although I think the Johns Hopkins Hospital in general is a very expensive place, a urinary culture costs only $2.00.

We did not have time—though it's all in the paper—to go into the dosage and the duration of treatment. Dr. Stearns says that he begins the treatment before a culture. We do, too, and that's one of the advantages of the sulfonamides, we think. The patient comes into the office miserably uncomfortable, with acute cystitis. We start her immediately on sulfonamides, but also make a culture. In case the sulfonamides don't work, then when we get the culture we know what antibiotic to use. Usually, however, the patient is well before we get the report of the culture.

One gentleman in the audienec asked me about the duration of therapy. We usually find that about five to six days of treatment with a sulfonamide is sufficient.

Dr. Stearns mentioned the proneness of patients to become sensitive to the antibiotics. Not only that, but the organisms are prone to become resistant to antibiotics, and we feel very strongly, therefore, that antibiotics should be used sparingly. If you use one of the antibiotics to treat a patient for an acute cold, as is frequently done, or for acute cystitis, and later on that patient gets pneumonia and has become sensitized to the antibiotic, a very serious situation may result. That is the reason that we feel these very effective and very valuable therapeutic agents are used much too promiscuously and indiscriminately.

(The papers presented at this meeting by Drs. Novak, Meigs, Brewer, and Cosbie will be published in the May issue.)

Items

American Board of Obstetrics and Gynecology

The Directors of the American Board of Obstetrics and Gynecology wish to express their thanks to the following gentlemen who responded so willingly to their request for help in proctoring the recent written examinations on Friday, Feb. 5, 1954:

Drs. Thomas M. Boulware, Birmingham, Ala.; George J. Mitchell, Mobile, Ala.; Archie E. Thomas, Montgomery, Ala.; Capt. H. J. Rickard (MC), USN, Seattle, Wash.; Drs. Willis E. Brown, Little Rock, Ark.; John F. McGill, Long Beach, Calif.; Lewis F. Boddie, Los Angeles, Calif.; Marvin G. Sadugor, Sacramento, Calif.; William B. McGee, San Diego, Calif.; Charles E. McLennan, San Francisco, Calif.; Richard K. Kerr, Colorado Springs, Colo.; Ben C. Williams, Denver, Colo.; Maurice I. Bakunin, Bridgeport, Conn.; Howard S. Morrow, Danbury, Conn.; Lewis P. James, Hartford, Conn.; Andrew A. Marchetti, Washington, D. C.; George H. H. Garrison, Wilmington, Del.; Donald M. Baldwin, Jacksonville, Fla.; R. F. Stover, Miami, Fla.; Courtlandt D. Berry, Orlando, Fla.; Samuel A. Manalan, West Palm Beach, Fla.; Charles B. Upshaw, Atlanta, Ga.; H. F. Sharpley, Jr., Savannah, Ga.; Colin C. McCorriston, Honolulu, T. H.; Verne J. Reynolds, Boise, Ida.; Carl Greenstein, Champaign, Ill.; F. H. Falls, Chicago, Ill.; Paul A. Raber, Decatur, Ill.; Mahlon F. Miller, Fort Wayne, Ind.; Charles F. Gillespie, Indianapolis, Ind.; Gordon C. Cook, South Bend, Ind.; Robert M. Collins, Council Bluffs, Iowa; Robert L. Newman, Kansas City, Kan.; George E. Cowles, Wichita, Kan.; Jennings B. Marshall, Louisville, Ky.; Jack R. Jones, Baton Rouge, La.; Max Mayo Miller, Lake Charles, La.; James Henry Ferguson, New Orleans, La.; Edwin E. Dilworth, Shreveport, La.; William A. Dodd, Baltimore, Md.; George A. Bourgeois, Boston, Mass.; Malcolm S. Allan, Springfield, Mass.; Ward F. Seeley, Detroit, Mich.; F. W. Tamblyn, Lansing, Mich.; Clarence E. Toshach, Saginaw, Mich.; Philip N. Bray, Duluth, Minn.; Titus P. Bellville, Minneapolis, Minn.; Lawrence M. Randall, Mayo Clinic, Rochester, Minn.; Richard Paddock, St. Louis, Mo.; Leonard A. Barrow, Billings, Mont.; Harley E. Anderson, Omaha, Neb.; S. A. Cosgrove, Jersey City, N. J.; A. Julius Gordon, Newark, N. J.; John D. Preece, Trenton, N. J.; Alton R. Pruit, Roswell, N. Mex.; John J. Gamble, Albany, N. Y.; Milton A. Carvalho, Binghamton, N. Y.; Benjamin I. Gilson, Brooklyn, N. Y.; Louis A. Trippe, Buffalo, N. Y.; John G. Hill, Jackson Heights, N. Y.; Theodore Neustaeder, New York, N. Y.; John F. Rogers, Poughkeepsie, N. Y.; Fred J. Fumia, Rochester, N. Y.; Albert W. Van Ness, Syracuse, N. Y.; Lewis S. Rathbun, Asheville, N. C.; J. Kingsley McDonald, Charlotte, N. C.; Saul Leighton Avner, Ft. Bragg, N. C.; Adlai S. Oliver, Raleigh, N. C.; J. H. Moore, Grand Forks, N. D.; Stanley T. Garber, Cincinnati, Ohio; Roger B. Scott, Cleveland, Ohio; James W. Norris, Columbus, Ohio; James B. Eskridge, Jr., Oklahoma City, Okla.; William F. Thomas, Jr., Tulsa, Okla.; Charles E. Hunt, Eugene, Ore.; Theodore M. Bischoff, Portland, Ore.; Charles K. Fetterhoff, Harrisburg, Pa.; Frank S. Deming, Philadelphia, Pa.; Auburn L. Baldwin, Pittsburgh, Pa.; Rafael A. Rivera Gil, Santurce, Puerto Rico; L. A. Wilson, Charleston, S. C.; Harold A. Schwartz, Chattanooga, Tenn.; Harry H. Jenkins, Knoxville, Tenn.; Orin L. Davidson, Jr., Memphis, Tenn.; Sam C. Cowan, Jr.; Nashville, Tenn.; Truman N. Morris, Austin, Texas; James T. Downs, III, Dallas, Texas; John W. Simpson, San Antonio, Texas; William A. McRoberts, Jr., Houston, Texas; D. D. Wall, San Angelo, Texas; Frank M. Posey, Jr., San Antonio, Texas; Vernon L. Ward, Ogden, Utah; John Z. Brown, Jr., Salt Lake City, Utah; Brock D. Jones, Jr., Norfolk, Va.; Joseph C. Parker, Richmond, Va.; Andrew M. Groseclose, Roanoke, Va.; Russell R. de Alvarez, Seattle,

Wash.; Harold E. Harrison (MC), USA, Tacoma, Wash.; Merrill Smeltzer, Walla Walla, Wash.; Franklin E. Kells, Wenatchee, Wash.; Edwin J. Humphrey, Huntington, W. Va.; R. E. Campbell, Madison, Wis.; Frederick J. Stoddard, Milwaukee, Wis.

The next scheduled examinations, Part II (oral and pathological), for all candidates will be held at the Edgewater Beach Hotel, Chicago, Ill., May 10 to 17, 1954. Formal notice of the exact time of each candidate's examination will be sent him several weeks in advance of the examinations.

Pan-Pacific Surgical Association

The Sixth Congress of the Pan-Pacific Surgical Association will be held in Honolulu, Hawaii, Oct. 7 and 8, 1954. Doctors are urged to make arrangements as soon as possible if they wish to be assured of adequate facilities.

The scientific program will be presented by over 100 leading surgeons, with sessions in all divisions of surgery and related fields. A social program is being developed for the doctors' families.

The Association office has been appointed as travel agent for those attending the Congress. All hotel and travel reservations must be made through the Honolulu headquarters of the Pan-Pacific Surgical Association.

For further information, write to F. J. Pinkerton, M.D., Director General, Pan-Pacific Surgical Association, Suite Seven, Young Building, Honolulu, Hawaii.